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*Profile, screening and progression*

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Emma Beeldman

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aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
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ten overstaan van een door het College voor Promoties ingestelde commissie,
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## CONTENTS

# 1

## Introduction

Motor neuron disease (MND), consisting of amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS), is a relentlessly progressive disease in which central and/or peripheral motor neuron degeneration leads to atrophy and muscle weakness, including respiratory and bulbar dysfunction. Death follows within 3 to 5 years from symptom onset in ALS, mostly as a result of respiratory insufficiency.[1] The disease course of PMA and especially PLS is less progressive.[2] In the Netherlands, approximately 1,500 people are suffering from ALS.[3] To date there is no cure and the only available drug in the Netherlands (Riluzole) extends life with 3 months.[4] Current treatment strategies are therefore based on physical and mental support and advance care planning.[5] In the Netherlands, multidisciplinary care for MND patients is coordinated by the Rehabilitation Medicine departments in specialized MND centers. Patients with severe respiratory insufficiency are offered non-invasive ventilation and patients with swallowing problems can opt for percutaneous endoscopic gastrostomy. The research presented in this thesis will focus on ALS, as this is the most frequent variant of MND.

**ALS and frontotemporal dementia**

In the past, ALS was considered to be a pure motor neuron disease in which other brain structures, such as those associated with cognition and behaviour, are not affected. However, the last decades it has become clear that a disease continuum exists with ALS and frontotemporal dementia (FTD) on both ends.[6, 7] Approximately 10 percent of ALS patients have or develop the behavioural variant of FTD (bvFTD).[8] BvFTD is characterized by progressive character changes: patients become disinhibited or apathetic and show a lack of empathy and disease insight.[9] Cognitive impairment can occur in bvFTD but is not an essential feature for the diagnosis.[9] When present, cognitive deficits are mostly seen in the domains social cognition, executive functions and language.[9] The overlap between ALS and FTD has been established clinically, but is also supported by genetic findings. In 2011, a hexanucleotide repeat expansion was discovered on the chromosome 9 open reading frame 72 (C9orf72) gene which is responsible for up to 40% of familial ALS and bvFTD cases.[10, 11] Other mutations (TAR DNA-binding protein (TDP43), superoxide dismutase 1 (SOD1) and RNA binding protein Fused in Sarcoma (FUS)) account for an extra 30% of familial ALS and FTD cases.[1] Brain imaging abnormalities and pathological changes in the frontotemporal lobes in a proportion of patients with ALS further support the existence of an ALS-FTD disease continuum.[12, 13]

**Cognitive and behavioural impairment in ALS**

Although only a small proportion (~10%) of ALS patients develops frontotemporal dementia, a larger group, approximately 30-60% has mild cognitive or behavioural impairment.[14-16] Examining cognitive and behavioural





impairment in ALS patients poses multiple problems. Due to motor impairment and speech disturbances, cognitive tests might be difficult to complete and the interpretation of results can be hampered. This could lead to an overestimation of cognitive impairment.[17, 18] Also, examining cognition requires a lengthy neuropsychological examination administered by a neuropsychologist, which is not available in every clinic. Behavioural impairment can be overestimated as immobility might be mistaken for apathy, and grief might lead to more withdrawn behaviour. Behaviour is typically explored in an in-depth interview with a proxy, which can be emotionally confronting. Therefore, adapted screening instruments for both cognitive and behavioural impairment, which are concise and possibly less confronting, are necessary.

Even though mild cognitive and behavioural impairment is harder to detect than frank bvFTD, it could have significant consequences. First, ALS-FTD patients are less compliant with therapy and therefore experience more difficulties with adherence to life-prolonging therapies, such as non-invasive ventilation.[19] However, it is not yet known whether this also applies to patients with mild cognitive or behavioural impairment. If so, this could negatively affect survival in this subpopulation. Second, cognitive and behavioural impairment negatively influences caregiver burden and quality of life of the caregiver. However, the influence on quality of life of the patient it not yet clarified.[19]

Hence, the consequences of mild cognitive and behavioural impairment in ALS are not yet clear. Another complex and unresolved issue is the course of mild cognitive and behavioural impairment. It is assumed to be a precursor of full-blown FTD, but this has not been consistently found.[14, 20-25] It is important to obtain a better understanding of the course of cognitive and behavioural impairment, not only for information supply to the patient and caregiver, but also to adjust supportive treatment strategies and advance care planning. It could also contribute to unravelling the pathophysiology of ALS.

The diverse estimates of the frequency and the scarcity of information on the course of cognitive and behavioural impairment in ALS, in combination with the lack of valid screening methods has led to the research presented in this thesis.

## Aims of this thesis

The main aim of this thesis was to develop tools for the detection of cognitive and behavioural impairment in ALS. The secondary aim was to investigate the

frequency, profile and course of cognitive and behavioural impairment in ALS patients.

These aims resulted in the following research questions:
1. What is the cognitive profile of ALS and is this similar to the cognitive profile of bvFTD?
2. Which behavioural changes most frequently occur in ALS?
3. How can we screen for cognitive and behavioural impairment in ALS patients, avoiding bias from motor and speech disturbances?
4. Are cognitive and behavioural impairment progressive in ALS and what is the impact on survival?

## Outline and hypotheses

**Part 1. Cognitive and behavioural impairment in ALS and behavioural variant FTD**

The frequency of cognitive impairment in ALS as described in the literature ranges from approximately 30 to 60%.[16, 26-28] This range may partly be related to the examination of different cognitive domains across studies. In 2010, we performed a meta-analysis of the cognitive profile of ALS, including 16 studies describing 554 ALS patients and found wide confidence intervals for most cognitive domains. Since 2010, many studies examining cognition in ALS have been published, including studies on social cognition, which is a relatively new cognitive domain. We hypothesized that the inclusion of a larger number of studies in the meta-analysis would result in a better-defined and comprehensive cognitive profile. In **chapter 2** we therefore present an update of the meta-analysis. As described above, there is clinical, genetic, imaging and pathological support for an overlap of ALS and behavioural variant frontotemporal dementia. However, a diagnosis of bvFTD does not require cognitive impairment and is mostly based on decline in behaviour. This is reflected by little knowledge about the cognitive profile of bvFTD. In **chapter 3** we present a meta-analysis on the cognitive profile of bvFTD and compare this profile to that of ALS. We expected to find a significant overlap between the two cognitive profiles.

There are multiple subtypes of bvFTD, including the apathetic and disinhibited type, which are characterized by different behavioural symptoms. It is not completely known which behavioural symptoms occur most often in ALS and whether the behavioural profile of ALS truly resembles that of bvFTD. Therefore, in **chapter 4** we provide a systematic overview of the literature on behavioural symptoms in patients with motor neuron disease and concomitant bvFTD.







**Part 2. Screening for cognitive and behavioural impairment**

The gold standard for cognitive impairment is a complete neuropsychological examination, which covers all cognitive domains and enables to determine the exact profile of cognitive impairment. However, this is a lengthy examination (about 2-3 hours) that is not available in every clinic and the performance on cognitive tests should be corrected for physical and speech disturbances, if present. Therefore, in ALS clinics, but also in clinical studies, cognitive screening tools are frequently used. However, many of these tools, such as the Mini Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) are not specifically developed for ALS patients and do not correct for physical impairment. Correction for physical impairment can prevent overestimation of cognitive deficits. An example of a cognitive test that is prone to bias due to slurred speech or impaired dexterity is the verbal fluency test (spoken or written, task consists of naming as many words starting with the same letter in one minute), which is frequently used in ALS patients. To correct for physical impairment, the verbal fluency index was developed, which reflects the thinking time per word of the fluency test. In **chapter 5** we provide normative data of the Dutch verbal fluency index.

In **chapter 6** we present a new cognitive screening tool for ALS patients, including a comparison with the Edinburgh Cognitive and Behavioural ALS Screen. We expected to find a high sensitivity of our new screen, because the cognitive tests included in the screen cover the cognitive profile of ALS.

In **chapter 7** we show the clinimetric properties of the ALS-FTD-Questionnaire, a questionnaire designed for the detection of behavioural impairment in ALS patients. The selection of items included in the questionnaire is based on the systematic review presented in **chapter 4** and we therefore expected to show good clinimetric properties.

**Part 3. Course and implications of cognitive and behavioural impairment**

The course of cognitive and behavioural impairment in ALS patients has not been completely elucidated. Some studies show evidence of progression of deficits over time, but other studies show stable impairment or even improvement at follow-up.[14, 20-25] Most of these studies investigated a cohort of so-called prevalent ALS patients, that is patients with diverging disease duration and disease stages, and some studies did not perform a complete neuropsychological examination.[23-25, 29-31] We hypothesized that, given the fast neurodegeneration in both ALS and bvFTD, cognitive and behavioural impairment in ALS would progress over time, especially when it is investigated in a cohort of ALS patients with a short disease duration. In **chapter 8** we

describe the results of neuropsychological examinations in a cohort of 'early' ALS patients, with a disease duration of less than 12 months, with follow-up measurements after 6 months, in order to examine the course of cognitive and behavioural impairment.

As described above, patients with ALS-FTD have difficulties with therapy compliance, including the use of non-invasive ventilation, which could result in a shorter survival.[19] It is conceivable that this also applies to ALS patients with mild cognitive and behavioural impairment. In **chapter 9** we therefore investigate the use of non-invasive ventilation in a cohort of prevalent MND patients with and without cognitive and behavioural impairment and its influence on survival.







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# PART 1

## Cognitive and behavioural impairment in ALS and behavioural variant FTD

# 2

## The cognitive profile of ALS: a systematic review and meta-analysis update

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## ABSTRACT

Cognitive impairment is present in approximately 30% of patients with amyotrophic lateral sclerosis (ALS) and, especially when severe, has a negative impact on survival and caregiver burden. Our 2010 meta-analysis of the cognitive profile of ALS showed impairment of fluency, executive function, language and memory. However, the limited number of studies resulted in large confidence intervals. To obtain a more valid assessment we updated the meta-analysis and included methodological improvements (controlled data extraction, risk of bias analysis and effect size calculation of individual neuropsychological tests). Embase, Medline and PsycInfo were searched for neuropsychological studies of non-demented patients with ALS and age-matched and education-matched healthy controls. Neuropsychological tests were categorised in 13 cognitive domains and effect sizes (Hedges' g) were calculated for each domain and for individual tests administered in ≥5 studies. Subgroup analyses were performed to assess the influence of clinical and demographic variables. Forty-four studies were included comprising 1287 patients and 1130 healthy controls. All cognitive domains, except visuoperceptive functions, showed significant effect sizes, compared to controls. Cognitive domains without bias due to motor impairment showed medium effect sizes (95% CI): fluency (0.56 (0.43 to 0.70)), language (0.56 (0.40 to 0.72)), social cognition (0.55 (0.34 to 0.76)), or small effect sizes: delayed verbal memory 0.47 (0.27 to 0.68)) and executive functions (0.41 (0.27 to 0.55)). Individual neuropsychological tests showed diverging effect sizes, which could be explained by bias due to motor impairment. Subgroup analyses showed no influence of bulbar disease onset and depression and anxiety on the cognitive outcomes. The cognitive profile of ALS consists of deficits in fluency, language, social cognition, executive functions and verbal memory. Social cognition is a new cognitive domain with a relatively large effect size, highlighting the overlap between ALS and frontotemporal dementia. The diverging effect sizes for individual neuropsychological tests show the importance of correction for motor impairment in patients with ALS. These findings have implications for bedside testing, the design of cognitive screening measures and full neuropsychological examinations.






## INTRODUCTION

Cognitive impairment occurs in approximately 30% of patients with amyotrophic lateral sclerosis patients (ALS) and a small proportion of patients (±10%) has frontotemporal dementia, mostly the behavioural variant.[1, 2] Cognitive impairment, especially when severe, bears significant implications for patients with ALS and their families: it increases caregiver burden and reduces survival which may be related to restricted use of non-invasive ventilation.[3, 4] More insight in the cognitive profile of ALS could lead to better bedside testing and more adequate information to the patient and their caregiver.

Across studies, deficits have been shown in different cognitive domains. Most consistently, executive dysfunction and fluency deficits are found.[5] There is increasing evidence of language impairment and memory dysfunction in patients with ALS and recently, impairment of social cognition has been shown.[6, 7] In 2008, we performed a meta-analysis of the cognitive profile of patients with ALS without dementia (n=16 studies, 554 patients, published in 2010) showing impairment of fluency, executive functions, language and memory.[8] For other cognitive domains, we were unable to draw firm conclusions due to limited data. Since 2008, many neuropsychological ALS studies have been published. With an update of the meta-analysis, we aimed to generate a more precise assessment of the cognitive profile of ALS.

## METHODS

### Search strategy

We searched Embase (1970-2014), Medline (1966-2014) and PsycInfo (1970-2014) up to 28 November 2014 for articles written in English, German, French or Dutch. References of articles were also considered for inclusion. Key words included ALS and its synonyms, cognition and frontotemporal dementia (supplementary table S1). Two authors (EB, MKT) performed title/abstract screening and subsequently full text evaluation. Consensus meetings led to the inclusion or exclusion of articles.

**Study selection**
Eligible articles were controlled studies. In case of longitudinal studies, only data from the first visit were used for analysis. All studies had to meet the following criteria:

- Patients had to be diagnosed with ALS according to the validated El Escorial criteria[9], that is, presence of a combination of upper and lower motor neuron signs. When patients with progressive muscular atrophy or primary lateral sclerosis were also studied, data of patients with ALS had to be reported separately.
- Patients and controls had to be matched for age and education, or age-corrected and education-corrected standard scores had to be used.
- Patients and controls had to be free of frontotemporal dementia and Alzheimer's disease, according to standard clinical criteria[10, 11] or according to the authors' statement. If demented participants were included in the study, the results of non-demented participants had to be reported separately.
- Data of at least one validated neuropsychological test had to be reported for both patients and controls as the mean and SD of raw or standardised test scores.
- Studies had to report unique cohorts. If studies reported data of the same cohort, the study with the largest sample was included.
- Studies had to correct for the presence of dysarthria or motor disabilities, or both, for example, use of adjusted neuropsychological tests or excluding patients with severe motor disabilities.

There were no exclusion criteria.

**Data extraction**
We extracted demographic and clinical variables from the articles: age (years), educational level (years of formal education), disease duration (months), site of onset (% bulbar onset), disease severity (ALS functional rating scale revised (ALSFRS-R))[12], respiratory function (forced vital capacity (FVC, percentage predicted (%pred.)) or $pCO_2$, capillary/arterial blood gas), use of psychoactive medication and depression/anxiety. In order to facilitate the interpretation of data, we categorised neuropsychological tests in 13 cognitive domains, as described before, that is, language, executive functions, fluency, immediate verbal memory, delayed verbal memory, visual memory, visuoperceptive functions, visuoconstructive functions, verbal IQ, psychomotor speed and attention. Owing to the widespread use of the Mini Mental State Examination (MMSE) in ALS studies, we included this test as a global measure of cognitive impairment. Social cognition was a new cognitive domain and was not included in the 2010 meta-analysis. Two of the authors (EB, MKT) performed the data extraction in order to reduce extraction errors.[13]







**Heterogeneity**
Subgroup analyses were performed to find explanations for moderate or substantial heterogeneity in the cognitive domains. The following demographic and clinical variables were assessed in the subgroup analyses: age (years), educational level (years of formal education), disease duration (months), site of onset (% bulbar onset), disease severity (ALSFRS-R), respiratory function, psychoactive medication use and depression/anxiety. For each variable, the studies were divided in two groups, based on a median split, except for respiratory function, use of psychoactive medication and depression/anxiety. Respiratory dysfunction and psychoactive medication use were not part of the exclusion criteria in all studies. For respiratory dysfunction, studies were divided in a group of "studies which excluded patients with severe respiratory dysfunction" and a second group of "studies which did not exclude patients with severe respiratory dysfunction or did not present data on respiratory function". For psychoactive medication use, studies were divided in a group of "studies which excluded patients with psychoactive medication use" and a second group of "studies which did not exclude patients with psychoactive medication use or did not present data on psychoactive medication use". For depression/anxiety, the studies were divided in a group with "depression/anxiety level comparable to healthy controls" and a group with "depression/anxiety level higher than healthy controls".

**Statistical analysis**
We calculated effect sizes, expressed as Hedges' g, per cognitive domain for each study, using Review Manager.[14] Hedges' g represents the mean difference between patients with ALS and healthy controls, divided by the pooled SD. When studies used multiple neuropsychological tests in one cognitive domain, an averaged effect size was computed in order to ascertain that each study only added one effect size to the final analysis.

We chose a random effects model to obtain an average weighted effect size across the studies. Effect sizes are considered small, medium and large when they are 0.2, 0.5 and 0.8, respectively.[15] A positive effect size, that is, an effect size of more than 0, indicates impaired performance of patients with ALS compared with healthy controls. An effect size was considered 'significant' when the CI did not contain 0. Effect sizes of individual cognitive tests were also calculated, when administered in ≥ 5 studies.

Statistical heterogeneity among studies was assessed with the Cochran's Q test (significance set at $p < 0.10$) and the $I^2$ statistic. $I^2$ describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Cut-off points for low, moderate and substantial heterogeneity are

25%, 50% and 75%, respectively.[16] Outliers within the domains with substantial heterogeneity were identified and effect sizes were recalculated after exclusion of the outlier.

### Risk of bias

One of the authors (EB) assessed the quality of included articles with the Newcastle – Ottawa quality assessment scale (NOS, maximum score 9 points).[17] The NOS evaluated the following aspects: selection of participants, comparability of the participants and data collection. Owing to the design of the included studies, that is, not blinded to the status of the participant, studies could not be awarded a point on the item 'ascertainment of exposure', and the maximum score was therefore eight points. The risk of selection bias was evaluated with a subgroup analysis, comparing studies with consecutively recruited patients to studies with a potential selection bias.

The risk of bias due to motor impairment and/or speech difficulties was assessed. Effect sizes were recalculated after exclusion of cognitive tests that require fine motor skills or normal speech; these recalculated (non-motor dependent) effect sizes were compared with the original effect sizes.

The presence of publication bias can result in a (more) significant mean effect size, because non-significant studies are less likely to be published. To investigate the probability of a relevant publication bias, we calculated the fail-safe N for all cognitive domains, that is, the number of studies without an effect which should be added to the meta-analysis to obtain a non-significant effect size, i.e. p=0.05.[18] A more conservative estimate of existing unpublished or unretrieved studies is the tolerance level ((5×number of studies examining the domain) + 10). If the fail-safe N is large in comparison to the tolerance level, the observed result is considered to be a reliable estimate of the real effect.

We used IBM Statistics SPSS, V.20 and Review Manager, V.5.2 for statistical analysis.

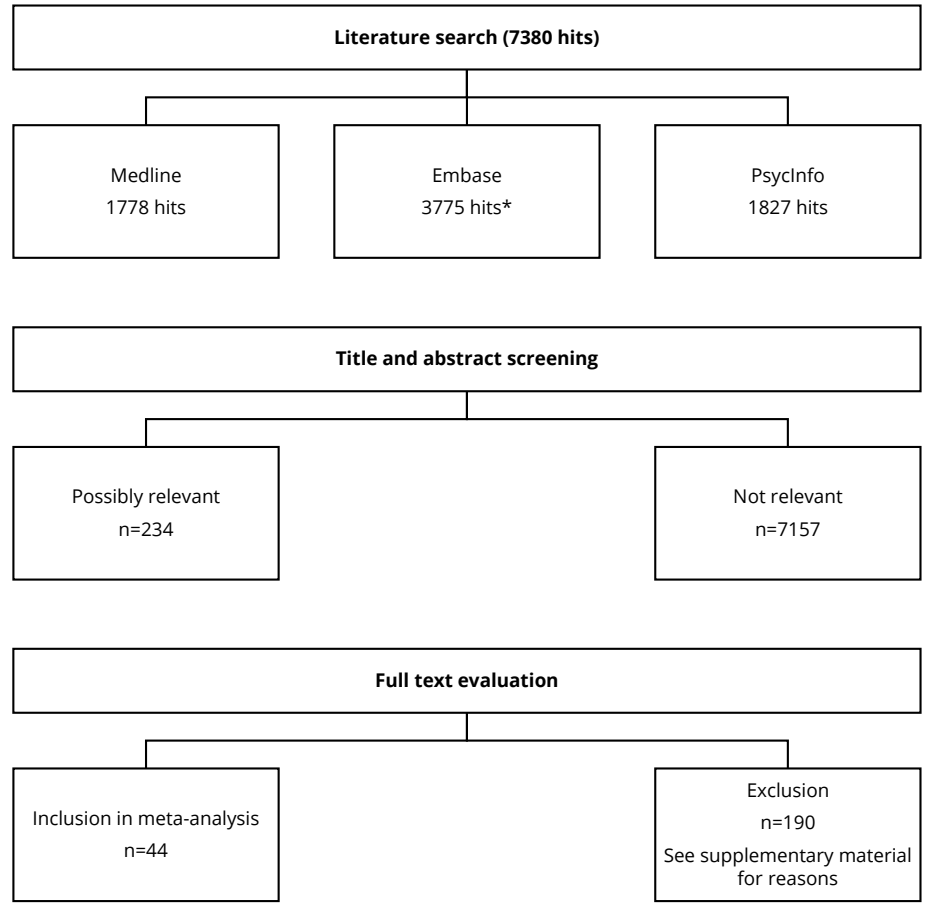
## RESULTS

The literature search yielded 7380 hits and 44 studies were included in this meta-analysis. Thirty studies were new compared to our previous meta-analysis (table 1 and figure 1). For an overview of the excluded articles and reasons for exclusion, see supplementary table S2.





**Figure 1.** Flow chart of literature search and study selection




Embase, Medline and PsycInfo were searched simultaneously with the same key words. *The flow chart shows the results after deduplication.

**Table 1.** Study characteristics of included articles

| ID | Author, year | NOS | Participants (patients/ controls) | Age, years (SD or range) | Education (years) | Diagnostic category | Onset (bulbar/ spinal) | Duration (months) | Disease severity | Depression / anxiety |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | David, 1986 | 6 | 14/9 | 53.7 (8.0) | - | - | 7/7 | 17.8 | - | - |
| 2 | Gallassi, 1989 | 6 | 18/36 | 55.7 (10.9) | 7.4 | - | - | 17.2 | - | - |
| 3 | Ludolph, 1992 | 6 | 17/17 | 58.5 (11.6) | - | - | 13/8 | - | - | 7.6 (5.7)[f] |
| 4 | Kew, 1993 | 7 | 16/16 | 59.1 (37-71) | - | Prob/def | 8/8 | 21.4 | - | - |
| 5 | Abrahams, 1997 | 6 | 52/28 | 57.2 (11.8) | 13.3 | Poss/prob | 24/28 | 22.3 | 31.8 (4.8)[b] | 9.8 (4.4)[e] |
| 6 | Rakowicz, 1998 | 7 | 15/24 | 68.3 (11.2) | 9.9 | Prob/def | 12/3 | 12.9 | - | - |
| 7 | Vieregge, 1999 | 6 | 8/8 | 54.2 (9.6) | 9.6 | Prob/def | 7/1 | 26.0 | 29.0 (12.0)[a] | 60.4 (5.3)[j] |
| 8 | McCullagh, 1999 | 7 | 18/10 | 62.3 (8.3) | 12.1 | Def | - | - | - | 6.3 (3.5)[e] |
| 9 | Abrahams, 2000 | 6 | 22/25 | 58.4 (10.6) | 14.1 | Poss | - | 25.9 | 32.2 (4.4)[b] | 6.8 (3.3)[e] |
| 10 | Hanagasi, 2002 | 5 | 20/13 | 55.8 (10.2) | 8.7 | Prob/def | 0/20 | 18.3 | 33.0 (2.5)[a] | 3.3 (2.3)[g] |
| 11 | Evdokimidis, 2002 | 6 | 51/28 | 58.8 (10.2) | 9.4 | - | 11/40 | 25.5 | 69.2 (25.0)[c] | - |
| 12 | Abrahams, 2004 | 6 | 28/18 | 53.0 (11.0) | 12.7 | Prob/def | - | 21.0 | - | 6.4 (3.5)[e] |
| 13 | Kilani, 2004 | 7 | 19/19 | 57.3 (11.1) | 12 | Prob/def | 2/17 | 24.0 | - | - |
| 14 | Papps, 2005 | 6 | 19/20 | 55.7 (11.7) | - | Prob/def | - | - | - | 8.5 (4.1)[e] |
| 15 | Ringholz, 2005 | 7 | 226/129 | - | 13.8 | Prob/def | - | 16.5 | 68.4 (20.5)[c] | 7.8 (6.0)[h] |
| 16 | Lulé, 2005 | 5 | 12/18 | 59.0 (9.0) | 12.6 | Prob/def | 0/12 | 40.0 | 75.5 (12.6)[d] | 8.9 (4.1)[f] |
| 17 | Rottig, 2006 | 7 | 15/15 | 58.8 (14.4) | - | - | 0/15 | 30.3 | - | - |
| 18 | Gibbons, 2007 | 6 | 16/16 | 60.8 (8) | 13 | - | 3/13 | 24.0 | - | - |
| 19 | Mezzapesa, 2007 | 5 | 16/9 | 62.0 (10.0) | 8.7 | Prob/def | - | 38.1 | 27.4 (8.6)[a] | - |
| 20 | Lulé, 2007 | 5 | 13/15 | 57.5 (10.5) | - | Prob/def | 0/14 | 23.0 | 36.8 (8)[a] | 12.7 (5.1)[f] |

**Table 1.** Continued.

| ID | Author, year | NOS | Participants (patients/ controls) | Age, years (SD or range) | Education (years) | Diagnostic category | Onset (bulbar/ spinal) | Duration (months) | Disease severity | Depression / anxiety |
|---|---|---|---|---|---|---|---|---|---|---|
| 21 | Raggi, 2008 | 5 | 10/10 | 64.7 (8.07) | 8.2 | Def | - | 42.9 | 28.4 (4.0)[b] | 1.1 (1.3)[g] |
| 22 | Lakerveld, 2008 | 7 | 11/11 | 52.3 (10.4) | 15 | - | - | 80.0 | 11.9 (8.2[a] | 21 (5.1)[j] |
| 23 | Ogawa, 2009 | 5 | 19/19 | 67.7 (7.4) | 10.3 | Def | 11/8 | 8.1 | - | 10.7 (6.5)[f] |
| 24 | Meier, 2010 | 8 | 18/18 | 64.5 (11.5) | 13.2 | Prob/def | - | 34.6 | 35.8 (5.2)[a] | 7.8 (3.6)[e] |
| 25 | Tsuji-Akimoto, 2010 | 6 | 18/16 | 65.4 (11.5) | 10.8 | Poss/prob/def | - | 19.4 | 34.7 (7.5)[a] | - |
| 26 | Volpato, 2010 | 5 | 24/17 | 54.8 (13.4) | 10.4 | Prob/def | 3/21 | 37.4 | 34.3 (6.9)[a] | 11.8 (3.8)[f] |
| 27 | Palmieri, 2010 | 5 | 9/10 | 51.7 (11.5) | 8.9 | Prob/def | - | 24.0 | - | 10.4 (2.1)[f] |
| 28 | Raaphorst, 2011 | 6 | 30/24 | 61.2 (11.8) | 13.8 | Prob/def | 10/20 | 21.5 | 40.3 (4.6)[a] | 8.6 (5.8)[e] |
| 29 | Cavallo, 2011 | 6 | 15/21 | 61.0 (10.0) | 14.9 | Prob/def | 1/14 | 32.2 | 31.3 (7.3)[a] | 5.7 (3.2)[e] |
| 30.1 | Girardi, 2011, part 1 | 6 | 19/20 | 56.1 (8.3) | 13.1 | Prob/def | - | 33.2 | 29.4 (10.5)[a] | 9.7 (3.6)[e] |
| 30.2 | Girardi, 2011, part 2 | 6 | 14/20 | 57.4 (16) | 14.4 | Prob/def | - | 38.1 | 29.8 (10.6)[a] | - |
| 31 | Sarro, 2011 | 5 | 16/15 | 61.0 (10.0) | 9 | Prob/def | 1/13 | 29.0 | 33.0 (7.0)[a] | - |
| 32 | Christidi, 2012 | 5 | 22/22 | 59.1 (17.6) | 9 | - | 8/14 | 19.2 | 37.5 (7.1)[a] | - |
| 33 | Cuddy, 2012 | 7 | 19/19 | 63.3 (9.1) | - | Prob/def | - | - | 37.7 (6.4)[a] | 3.4 (2.9)[e] |
| 34 | Palmieri, 2012 | 6 | 24/27 | 61.6 (9.5) | 9.4 | Prob/def | 8/16 | 13.0 | 40.4 (5.1)[a] | 13.9 (8.5)[f] |
| 35 | Phukan, 2012 | 7 | 132/110 | 62.7 (9.5) | 12.2 | Poss/prob/def | - | - | - | 8.0 (4.9)[e] |
| 36 | Roberts-South, 2012 | 6 | 16/12 | 52.8 (9.2) | 14.9 | - | 5/11 | - | - | - |
| 37 | Zalonis, 2012 | 6 | 48/47 | 60.3 (11.2) | 9.7 | - | 18/30 | 21.0 | 27.7 (4.1)[a] | - |

**Table 1.** Continued.

| ID | Author, year | NOS | Participants (patients/ controls) | Age, years (SD or range) | Education (years) | Diagnostic category | Onset (bulbar/ spinal) | Duration (months) | Disease severity | Depression / anxiety |
|---|---|---|---|---|---|---|---|---|---|---|
| 38 | Christidi, 2013 | 5 | 26/26 | 61.4 (10.4) | 11.4 | - | 8/18 | 21.9 | 28.9 (4.1)[a] | - |
| 39 | Taylor, 2013 | 6 | 51/35 | 59.8 (9.1) | 13.8 | Prob/def | 13/38 | - | 33.2 (9.1)[a] | 8.3 (5.8)[e] |
| 40 | Fiori, 2013 | 5 | 23/23 | 56.6 (12.4) | 14.5 | Prob/def | 19/4 | 19.8 | 22.8 (10.9)[a] | - |
| 41 | Hu, 2013 | 5 | 27/43 | 57.7 (10.4) | 15.2 | Poss/prob/def | - | - | - | - |
| 42 | Savage, 2013 | 5 | 13/30 | 58.0 (8.4) | 14.1 | Prob/def | 2/11 | - | 37.3 (3.1)[a] | - |
| 43 | Staios, 2013 | 7 | 35/30 | 63.5 (9.7) | - | Prob/def | - | 32.1 | 36.4 (9.0)[a] | 9.5 (4.3)[e] |
| 44 | Mannerelli, 2014 | 7 | 33/32 | 63.3 (10.3) | 9.7 | Prob/def | 11/22 | 21.0 | 35.8 (8.8)[a] | - |

Legend. ID: study number; NOS: Newcastle – Ottawa quality assessment scale for case-control studies; N: number of participants; diagnostic category: according to El Escorial criteria; poss: possible ALS; prob: probable ALS; def: definite ALS. Disease severity is measured with [a]ALSFRS-R, [b]ALSSS, [c]Appel scale and [d]Norris scale. The scores of the ALSFRS-R, ALSSS and Norris score range from 0 to 48, 40 and 100, respectively, which indicate no disability. The scores of the Appel score range between 30 and 164 and lower scores indicate less disability. Depression/anxiety is measured with [e]HADS, [f]BDI, [g]Hamilton, [h]GDS, [i]ALS depression Inventory and [j]the Von Zerssen depression scale. For a list of the included articles, see supplementary table S4.





### Study characteristics

A total of 1287 patients (62.8% males) and 1130 healthy controls (55.5% males) were included in the meta-analysis (table 1). In three studies only patients with definite ALS were analysed and in 26 studies patients had either probable or definite ALS. The mean age (SD) of the patients was 59.2 years (3.9) and the disease duration ranged from 8.1 to 80.0 months (median 23.5). The site of onset was reported in 28 studies (63.6% bulbar onset in 33% of patients), of which five included a higher proportion of bulbar onset than patients with limb onset. Disease severity was measured with different scales across studies, that is, the Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised (ALSFRS-R, maximum score 48 = no disability), the ALS severity scale (ALSSS, maximum score 40 = no disability), the Appel score (scores between 30 and 164, lower scores = less disability) and the Norris score (maximum score 100 = no disability).[12, 19-21] The ALSFRS-R was used most frequently (n=23 studies, 52.3%), with a median score (range) of 33.2 (11.9 – 40.4). The median scores (range) of the ALSSS, Appel score and Norris score were 31.8 (28.4-32.2), 68.8 (30-123) and 75.5 (50-92), respectively. In most studies, the disability scores indicated a mild to moderate disease severity. One study examined patients with an advanced disease state, with a mean (SD) ALSFRS-R of 11.9 (8.2).

Studies corrected for the presence of dysarthria and/or motor disabilities by using an adjusted neuropsychological test battery (time-dependent tests were excluded or tests were corrected for slowing of speech), by excluding patients with severe motor impairment or dysarthria, or some patients did not perform all tests due to motor impairment or dysarthria (supplementary table S3).

Twenty-one studies (47.7%) reported data on the presence of respiratory failure. Eight studies excluded patients with a FVC (%pred) below 70%, while two studies performed blood gas analysis to investigate the presence of hypercapnia. In 11 studies, patients had no severe respiratory dysfunction, as stated by the authors. Depression and anxiety were measured in 26 studies (59.1%), most frequently with the Hospital Anxiety and Depression Scale (HADS, 53.8%). Other depression and anxiety scales were the Beck Depression Inventory (BDI, n=7, max score 63)[22], the Hamilton Rating Scale for Depression (n=2, max score 52)[23], the ALS depression inventory (n=1, max score 48), the Geriatric Depression scale (n=1, max score 30)[24] and the Von Zerssen depression scale (n=1, max score 48)[25]. In the majority of the studies (72.7%), the scores did not differ between the patients with ALS and healthy volunteers. Six studies showed significantly more depressive and/or anxiety symptoms in patients with ALS compared to controls.

Twenty-one studies excluded patients if they used psychoactive medication, one study did not exclude patients, and the remaining 22 studies did not report medication use. References related to the abovementioned study characteristics can be found in supplementary table S4.

**Effect sizes of cognitive domains**

All cognitive domains, except visuoperceptive functions, showed significant effect sizes, that is, impairment in patients with ALS, compared with controls (figure 2). In the domains with little or no bias due to motor impairment, medium effect sizes were found, that is, between 0.5 and 0.8 for the domains fluency, language and social cognition (table 2). Small effect sizes, that is, below 0.5, were found for the domains delayed verbal memory, immediate verbal memory, attention, executive functions, verbal IQ and visual memory. The domains in which bias due to motor impairment could not be ruled out, i.e. visuoconstructive functions, psychomotor speed and MMSE, showed large or medium effect sizes. These domains were exclusively examined with time-dependent and motor-dependent tests and an adjusted effect size without motor bias could not be calculated.

The main differences with the results of our 2010 meta-analysis are the inclusion of social cognition as a new cognitive domain, the significant effect size of delayed verbal memory and narrow CIs (figure 2), due to the inclusion of more studies.

To reduce bias due to motor impairment, the effect sizes of the domains fluency, language, executive functions and visual memory were recalculated after exclusion of the time-dependent and motor-dependent tests, which did not considerably change the effect sizes of fluency, language and visual memory. The effect size of executive functions decreased after exclusion of the time-dependent and motor-dependent tests from 0.49 to 0.41 (table 2).

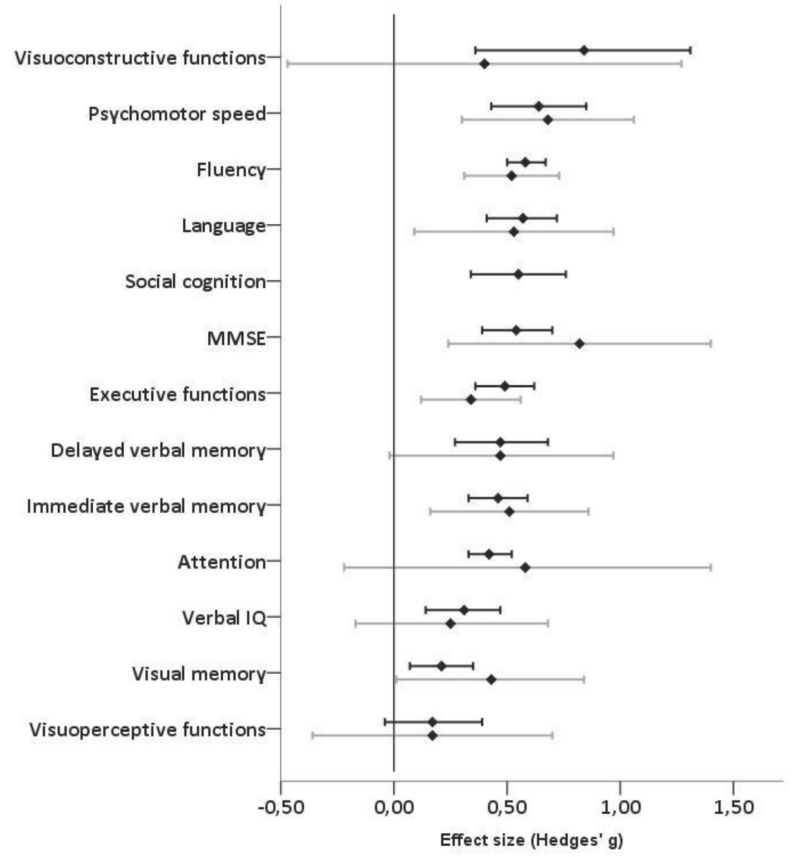
**Effect sizes of neuropsychological tests**

The neuropsychological tests used in each cognitive domain are listed in supplementary table S5. The largest effect sizes were found for the trail making test part B, colour word interference of the Stroop test, symbol digit modalities test, letter fluency, word-reading and colour-naming of the Stroop test and naming tests (table 2).





**Figure 2.** Effect size per cognitive domain




Effect size is expressed as Hedges' g, larger values indicate more impairment in patients with ALS compared to healthy volunteers. Black line: meta-analysis update; grey line: meta-analysis 2010. For a description of the neuropsychological tests included in each domain, see supplementary table S5. ALS, amyotrophic lateral sclerosis.

**Heterogeneity**

Heterogeneity was low in the domains MMSE, fluency, immediate verbal memory, attention, verbal IQ and visual memory (range $I^2$ values: 0-20%). Moderate heterogeneity ($I^2$: 43-50%) was found in the domains language, social cognition and visuoperceptive functions. The domains visuoconstructive functions, psychomotor speed, executive functions and delayed verbal memory showed substantial heterogeneity ($I^2$: 56-74%). In the domains visuoconstructive functions, psychomotor speed and delayed verbal memory, a main outlier could be identified, and effect sizes were recalculated after exclusion of the outlier (table 2).

**Table 2.** Pooled weighted effect sizes and heterogeneity statistics of all cognitive domains and frequently used neuropsychological tests

| Cognitive domain | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ | Fail-safe N | Tolerance level |
|---|---|---|---|---|---|---|---|---|---|
| **Visuoconstructive functions** | **0.84** | **0.36-1.31** | **6** | **202** | **15.42** | **0.009** | **68%** | **154** | **40** |
| Recalculation w/o outlier | 0.63 | 0.36-0.90 | 5 | 183 | 4.43 | 0.35 | 10% | n/a | n/a |
| **Psychomotor speed** | **0.64** | **0.43-0.85** | **16** | **613** | **34.90** | **0.003** | **57%** | **3493** | **90** |
| Recalculation w/o outlier | 0.69 | 0.49-0.89 | 15 | 561 | 25.69 | 0.03 | 46% | n/a | n/a |
| Neuropsychological tests | | | | | | | | | |
| TMT, part A | 0.50 | 0.23-0.76 | 8 | 332 | 9.34 | 0.23 | 25% | n/a | n/a |
| Stroop, part 1 and 2 | 0.62 | 0.24-1.00 | 6 | 234 | 19.44 | 0.002 | 74% | n/a | n/a |
| SDMT | 0.73 | 0.45-1.01 | 6 | 236 | 4.67 | 0.46 | 0% | n/a | n/a |
| **Fluency** | **0.58** | **0.50-0.67** | **25** | **1217** | **21.24** | **0.62** | **0%** | **39612** | **135** |
| Recalculation w/o motor bias | 0.56 | 0.43-0.70 | 12 | 761 | 12.97 | 0.30 | 15% | n/a | n/a |
| Neuropsychological tests | | | | | | | | | |
| Letter fluency | 0.68 | 0.55-0.82 | 23 | 1120 | 28.11 | 0.17 | 22% | n/a | n/a |
| Category fluency | 0.55 | 0.41-0.68 | 15 | 849 | 6.41 | 0.96 | 0% | n/a | n/a |
| **Language** | **0.57** | **0.41-0.72** | **19** | **810** | **31.46** | **0.03** | **43%** | **6897** | **105** |
| Recalculation w/o motor bias | 0.56 | 0.40-0.72 | 18 | 776 | 31.25 | 0.02 | 46% | n/a | n/a |
| Neuropsychological tests | | | | | | | | | |
| Naming test | 0.60 | 0.42-0.78 | 16 | 694 | 19.21 | 0.20 | 22% | n/a | n/a |
| **Social cognition** | **0.55** | **0.34-0.76** | **6** | **252** | **9.24** | **0.10** | **46%** | **358** | **40** |
| **MMSE** | **0.52** | **0.37-0.68** | **17** | **956** | **18.87** | **0.28** | **15%** | **4537** | **95** |
| **Executive functions** | **0.49** | **0.36-0.62** | **31** | **1587** | **117.16** | **<0.001** | **74%** | **18687** | **165** |
| Recalculation w/o motor bias | 0.41 | 0.27-0.55 | 22 | 1201 | 70.90 | <0.001 | 69% | n/a | n/a |
| Neuropsychological tests | | | | | | | | | |
| WCST | 0.50 | 0.28-0.72 | 17 | 698 | 90.25 | <0.001 | 82% | n/a | n/a |
| Stroop, part 3 | 0.75 | 0.30-1.20 | 14 | 813 | 117.44 | <0.001 | 89% | n/a | n/a |
| TMT, part B | 0.89 | 0.36-1.42 | 10 | 457 | 99.37 | <0.001 | 91% | n/a | n/a |
| Brixton | 0.18 | -0.27-0.63 | 5 | 463 | 18.37 | 0.001 | 78% | n/a | n/a |
| **Delayed verbal memory** | **0.47** | **0.27-0.68** | **16** | **640** | **33.81** | **0.004** | **56%** | **1900** | **90** |

**Table 2.** Continued.

| Cognitive domain | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ | Fail-safe N | Tolerance level |
|---|---|---|---|---|---|---|---|---|---|
| Recalculation w/o outlier | 0.52 | 0.32-0.72 | 15 | 586 | 25.14 | 0.03 | 44% | n/a | n/a |
| Neuropsychological tests | | | | | | | | | |
| AVLT | 0.47 | 0.21-0.74 | 11 | 460 | 23.05 | 0.01 | 57% | n/a | n/a |
| **Immediate verbal memory** | **0.46** | **0.33-0.59** | **19** | **755** | **22.39** | **0.21** | **20%** | **6916** | **110** |
| Neuropsychological tests | | | | | | | | | |
| AVLT | 0.58 | 0.33-0.82 | 9 | 358 | 12.16 | 0.14 | 34% | n/a | n/a |
| **Attention** | **0.42** | **0.33-0.52** | **14** | **1086** | **14.50** | **0.34** | **10%** | **5582** | **80** |
| Neuropsychological tests | | | | | | | | | |
| Digit span | 0.33 | 0.20-0.46 | 11 | 653 | 9.07 | 0.53 | 0% | n/a | n/a |
| **Verbal IQ** | **0.28** | **0.11-0.46** | **10** | **485** | **5.69** | **0.77** | **0%** | **470** | **60** |
| **Visual memory** | **0.21** | **0.07-0.35** | **17** | **593** | **14.79** | **0.54** | **0%** | **881** | **95** |
| Recalculation w/o motor bias | 0.23 | 0.08-0.38 | 14 | 463 | 12.63 | 0.48 | 0% | n/a | n/a |
| **Visuoperceptive functions** | **0.17** | **-0.04-0.39** | **9** | **404** | **15.96** | **0.04** | **50%** | **n/a** | **n/a** |

Legend. Hedges' g: effect size; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p-value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q – degrees of freedom / Q x 100%); Fail-safe N: number of non-significant studies needed to obtain a non-significant effect size (p=0.05), not calculated for visuoperceptive functions, because this domain showed no significant effect size; Tolerance level: estimated number of existing unpublished studies (5k+10); Recalculation w/o motor bias: effect size after exclusion of tests with possible bias due to motor impairment, w/o: without; Recalculation w/o outlier: effect size after exclusion of the main outlier in domains with substantial heterogeneity, w/o: without. For executive functions, no outlier could be identified. n/a: not applicable. Effect sizes of neuropsychological tests that were administered in ≥5 studies were also calculated. TMT: trail making test; Stroop, part 1 and 2: Word-reading and color-naming of the Stroop test; SDMT: symbol digit modalities test; WCST: Wisconsin card sorting test; Stroop, part 3: Color word interference of the Stroop test; Brixton: Brixton spatial anticipation test; AVLT: auditory verbal learning test.

### Subgroup analyses

There was no influence of site of onset on any of the cognitive domains (table 3). Disease severity or the presence of depressive and anxiety symptoms did not significantly contribute to the effect sizes on any of the cognitive domains (data not shown, but available on request). Studies with younger patients had more impairment of psychomotor speed. Studies with a lower educational level had more impairment of executive functions. A shorter disease duration resulted in more impairment of visual memory and immediate verbal memory. Studies that excluded patients with respiratory dysfunction showed less impairment of psychomotor speed, delayed verbal memory and MMSE. Studies that excluded patients with psychoactive medication showed less impairment of attention and visual memory.

**Table 3.** Subgroup analysis of the percentage of bulbar disease onset in the included studies

| Cognitive domain | Bulbar onset | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ |
|---|---|---|---|---|---|---|---|---|
| Visuoconstructive functions | < 32.3 | 0.83 | -0.04-1.70 | 2 | 85 | 0.62 | 0.43 | 0% |
| | > 32.3 | 0.44 | -0.02-0.89 | 2 | 76 | | | |
| Psychomotor speed | < 32.3 | 0.40 | 0.05-0.75 | 7 | 244 | 0.01 | 0.93 | 0% |
| | > 32.3 | 0.38 | 0.11-0.65 | 5 | 187 | | | |
| Fluency | < 32.3 | 0.65 | 0.49-0.82 | 8 | 313 | 0.06 | 0.80 | 0% |
| | > 32.3 | 0.69 | 0.48-0.89 | 7 | 291 | | | |
| Language | < 32.3 | 0.66 | 0.37-0.96 | 7 | 290 | 1.45 | 0.23 | 31.3% |
| | > 32.3 | 0.35 | -0.07-0.77 | 4 | 176 | | | |
| Social cognition | < 32.3 | 0.36 | -0.02-0.74 | 2 | 79 | n/a | n/a | n/a |
| | > 32.3 | n/a | n/a | 0 | 0 | | | |
| MMSE | < 32.3 | 0.53 | 0.20-0.86 | 7 | 230 | 0.00 | 0.99 | 0% |
| | > 32.3 | 0.53 | 0.32-0.74 | 5 | 563 | | | |
| Executive functions | < 32.3 | 0.56 | 0.39-0.73 | 10 | 447 | 0.00 | 0.97 | 0% |
| | > 32.3 | 0.57 | 0.19-0.95 | 9 | 429 | | | |
| Delayed verbal memory | < 32.3 | 0.51 | 0.16-0.86 | 6 | 222 | 0.23 | 0.63 | 0% |
| | > 32.3 | 0.38 | -0.03-0.78 | 6 | 268 | | | |
| Immediate verbal memory | < 32.3 | 0.43 | 0.21-0.65 | 6 | 222 | 0.65 | 0.42 | 0% |
| | > 32.3 | 0.57 | 0.31-0.82 | 5 | 224 | | | |
| Attention | < 32.3 | 0.36 | 0.16-0.56 | 4 | 160 | 1.40 | 0.24 | 28.5% |
| | > 32.3 | 0.50 | 0.38-0.63 | 9 | 531 | | | |
| Verbal IQ | < 32.3 | 0.21 | -0.01-0.44 | 3 | 161 | 0.42 | 0.52 | 0% |
| | > 32.3 | 0.33 | 0.05-0.62 | 6 | 290 | | | |
| Visual memory | < 32.3 | 0.11 | -0.12-0.34 | 7 | 269 | 2.01 | 0.16 | 50.3% |
| | > 32.3 | 0.35 | 0.12-0.58 | 4 | 179 | | | |
| Visuoperceptive functions | < 32.3 | 0.36 | -0.04-0.77 | 3 | 101 | 2.72 | 0.10 | 63.2% |
| | > 32.3 | 0.07 | -0.39-0.25 | 2 | 86 | | | |

Legend. Bulbar onset: percentage of patients with bulbar disease onset; Hedges' g: effect size; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p-value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q – degrees of freedom / Q x 100%); n/a: not applicable.





### Risk of bias

The representativeness of the patient cohort was infrequently stated (n=18). The subgroup analysis for selection bias showed no differences in effect sizes for any of the cognitive domains. The recruitment method of healthy volunteers was described in 26 studies. The non-response rate was also infrequently recorded (n=5). The fail-safe N exceeded the tolerance level at least five times in all cognitive domains, indicating that the mean effect sizes are a reliable estimate of the true value when publication bias is considered.

## DISCUSSION

We updated our meta-analysis of cognitive impairment of non-demented patients with ALS, compared with healthy volunteers. The cognitive profile of ALS consists of deficits in fluency, language, social cognition, executive functions and verbal memory.

### Social cognition and the overlap with FTD

Social cognition is a new cognitive domain compared to our previous meta-analysis and its effect size is comparable to the domains language and fluency. It includes recognition of the emotional states of others and insight into social situations and social protocol.[26, 27] This finding corroborates the overlap between ALS and FTD, as studies in FTD have shown extensive impairment of social cognition which is correlated to cortical atrophy of the right orbitofrontal, superior temporal, occipital and posterior cingulate regions.[26-28]

However, in order to investigate the existence of a cognitive continuum, neuropsychological studies are needed that directly compare patients with ALS, ALS-FTD and FTD. To the best of our knowledge, there are only three such studies. Two studies only administered the Addenbrooke's cognitive examination and therefore do not allow for a comparison of the cognitive profiles.[29, 30] Another study administered tests of social cognition, which showed similar scores of patients with ALS and healthy volunteers and comparable deficits in the ALS-FTD and FTD groups.[7] In the current meta-analysis, we excluded studies which examined patients with ALS-FTD, in order to assess the cognitive profile of patients with ALS without dementia and reduce the heterogeneity in the data. Subtle effects of mild cognitive impairment in a large ALS cohort might be overshadowed by large effects in a small ALS-FTD subgroup in the cohort. Also, the inclusion of patients with severe behavioural changes may lead to seemingly impaired performance on cognitive tests, due to a lack of attention and interest. Despite the challenges of examining

patients with ALS-FTD, neuropsychological studies are needed to elucidate the similarities and differences between ALS and FTD.

Associations between behavioural changes and cognitive impairment on the one hand and reduced survival and caregiver burden on the other hand have been found previously.[4, 31] Considering the prominent role of social cognition in this meta-analysis, social cognition deficits may also be associated with shorter survival and increased caregiver burden. This warrants more thorough investigation in future studies.

**Memory**

Our previous meta-analysis showed significant effect sizes for immediate verbal memory and visual memory, and a large CI for delayed verbal memory which did not reach significance. The current update shows significant effect sizes for all memory domains, with the largest effect size for delayed verbal memory. Although both the medial temporal lobe (MTL) and the prefrontal cortex are involved in delayed and immediate memory, delayed memory relies primarily on intact functioning of the MTL, whereas immediate memory is thought to be a function of the mid-dorsolateral frontal cortex.[32, 33] The finding of memory changes in our meta-analysis, therefore, could reflect changes in the MTL, which have been described as TDP-43 positive neuronal inclusions in the dentate gyrus, hippocampus and transentorhinal cortex, found in post mortem studies of patients with ALS, in particular when concomitant dementia was present.[34] Recent MRI studies underlined the involvement of the MTL in non-demented patients with ALS, by correlating hippocampal volume with impairment of verbal memory.[35, 36]

**Executive functions**

Although executive dysfunction is often found in patients with ALS, the effect size for this domain was smaller than for the domains language and social cognition.[6] This is probably related to our decision to examine fluency as a separate cognitive domain, for which we found a larger effect size, that is, 0.58 compared to 0.49. Furthermore, the neuropsychological tests of the executive domain showed diverging effect sizes, that is, the trail making test and the Stroop test showed large effect sizes, whereas the Brixton spatial anticipation test had a non-significant effect size. This could be explained by deficits in motor function and speech in patients with ALS. The tests with large effect sizes are time-dependent and require fine motor skills or normal speech and, when excluded from the analysis, executive functions had one of the smallest effect sizes. When examining patients with ALS, it is therefore key to administer tests that correct for physical impairment, in order to avoid overestimation of cognitive deficits.[37]







**Respiratory function**

Impairment of executive functions and memory (list and object learning) is known to be partially related to respiratory dysfunction in ALS and is thus partially reversible after initiation of night-time non-invasive ventilation.[38] In the current meta-analysis, only 10 out of 44 studies (22.7%) reported measurements of respiratory function which may have led to an overestimation of the effect sizes of the executive and memory domains. An exploratory subgroup analysis showed no effect of respiratory function on the majority of the cognitive domains, except for psychomotor speed, delayed verbal memory and MMSE. For a valid statement on the influence of respiratory dysfunction on cognitive function in ALS, more studies need to report detailed data about the presence or absence of respiratory dysfunction.

**Bulbar disease onset**

The relation between bulbar disease onset and cognitive impairment in ALS has been debated. The proportion of bulbar disease onset in incident ALS cohorts is approximately 33%, but ranges from 33% to 60% in cognitively impaired cohorts.[1, 39-41] With a subgroup analysis, we found no evidence of more severe cognitive deficits in patients with bulbar disease onset. The varying rates of bulbar disease onset in cognitively impaired cohorts may be related to the presence of dysarthria in combination with the use of time-dependent tests. A correction for slowing of speech is therefore essential.[37]

**Limitations**

In addition to its strengths, that is, a large number of patients, careful selection of articles, extraction of data by two individuals and a systematic analysis, this study has some limitations.

Bias due to motor impairment could not be ruled out in the domains visuoconstructive functions, MMSE and psychomotor speed, because these were exclusively examined with tests that require fine motor skills and/or normal speech. All studies corrected for severe motor impairment, but adjustments for mild motor impairment were often not performed. This might explain why the effect sizes of these domains were among the largest effect sizes, indicating that patients with ALS have more difficulty performing the motor part of these tests than healthy volunteers. However, the effect size of language, fluency and visual memory, which were partly examined with time-dependent or motor-dependent tests, did not change after exclusion of these tests. This implies that bias due to motor impairment was small in these three domains.

We included the MMSE in our analyses as a global measure of cognitive impairment. However, there are some limitations in the use of MMSE. First of

all, there is a large ceiling effect in the normal population, implying that healthy controls are likely to obtain (near) maximum scores.[42] Second, three items of MMSE require normal hand function, and could lead to an underestimation of the abilities of patients with ALS. The combination of the ceiling effect and the motor-dependent items in MMSE could have resulted in an artificially large difference between patients with ALS and healthy controls.

There was substantial heterogeneity in the domains visuoconstructive functions, psychomotor speed, executive functions and delayed verbal memory, hindering the interpretation of the results. The most likely explanation for the heterogeneity is the presence of outliers within these domains. For the domains visuoconstructive functions, psychomotor speed, and delayed verbal memory, a single outlier could be identified, and after exclusion, heterogeneity was reduced to 10%, 46% and 44%, respectively. For the domain executive functions, a single outlier could not be identified, but all individual studies, except one, showed impairment of patients with ALS, compared to healthy volunteers. Our results therefore indicate impairment of patients with ALS on executive function tasks, but the results of our study emphasize the importance of tests that correct for physical impairment and slowing of speech to avoid false positive results.

In conclusion, the cognitive profile of patients with ALS consists of deficits in fluency, language, social cognition, executive functions and verbal memory with sparing of visuoperception. These findings provide further support for the observation that the cognitive deficits of ALS are more than "just frontal", which has implications for bedside testing, the design of cognitive screening measures and full neuropsychological examinations.

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# SUPPLEMENTAL MATERIAL

**Table S1.** Key words used in the literature search

| | | |
|---|---|---|
| amyotrophic lateral sclerosis, ALS, motor neuron(e) disease, MND, Gehrig | **OR** | FTD, frontotemporal dementia, FTLD, pick's disease, frontal variant FTD, frontal variant dementia, bv-FTD, f-FTD, frontotemporal (lobar) degeneration, presenile dementia |
| | **AND** | |
| cognition, mild cognitive impairment, cognition disorders, language disorders, (neuro) psychological tests, language (tests), memory, MMSE, Mini Mental State Examination, theory of mind, Frontal Assessment Battery, Boston Naming, Wisconsin Card Sorting Test, Stroop test, trail making test, aptitude tests | | |

**Table S2.** Excluded studies

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Ash | Neurology | 2014 | ALS-FTD patients included in patient group |
| Grossman | JAMA Neurology | 2014 | ALS-FTD patients included in patient group |
| Hammer | Brain Research | 2011 | ALS-FTD patients included in patient group |
| Lepow | Journal of Clinical and Experimental Neuropsychology | 2010 | ALS-FTD patients included in patient group |
| Machts | BMC Neurology | 2014 | ALS-FTD patients included in patient group |
| Mioshi | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2014 | ALS-FTD patients included in patient group |
| Pettit | Brain Imaging and Behaviour | 2013 | ALS-FTD patients included in patient group |
| Schmolck | Neurology | 2007 | ALS-FTD patients included in patient group |
| Usman | American Journal of Neuroradiology | 2011 | ALS-FTD patients included in patient group |
| Vass | Acta Neuropathologica | 2011 | ALS-FTD patients included in patient group |
| Zimmerman | Cognitive Behavioral Neurology | 2007 | ALS-FTD patients included in patient group |
| Abdulla | Neurobiology of Aging | 2014 | Control group not matched for age/education |
| Abe | Neuroradiology | 2001 | Control group not matched for age/education |
| Ahmed | Journal of Neurology | 2014 | Control group not matched for age/education |
| Ayaz | Journal of Neuroscience and Neuroengineering | 2014 | Control group not matched for age/education |
| Blain-Moraes | Neurscience Letters | 2013 | Control group not matched for age/education |
| Brown | Psychosomatic Medicine | 1970 | Control group not matched for age/education |
| Burrell | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2013 | Control group not matched for age/education |
| Donaghy | Journal of Neurology | 2009 | Control group not matched for age/education |
| Jelsone-Swain | Frontiers in Psychology | 2012 | Control group not matched for age/education |
| Kolind | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2013 | Control group not matched for age/education |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Kuruvilla | Cognitive Neuroscience | 2013 | Control group not matched for age/education |
| Lulé | Journal of Neurology, Neurosurgery & Psychiatry | 2010 | Control group not matched for age/education |
| Menke | Brain Imaging and Behaviour | 2014 | Control group not matched for age/education |
| Morimoto | Journal of the Neurological sciences | 2012 | Control group not matched for age/education |
| Pinkhardt | Journal of Neurology | 2008 | Control group not matched for age/education |
| Piquard | Psychologie et Neuropsychiatrie du Vieillissement | 2010 | Control group not matched for age/education |
| Poujois | Human Brain Mapping | 2013 | Control group not matched for age/education |
| Real | Clinical Neurophysiology | 2014 | Control group not matched for age/education |
| Shaunak | Annals of Neurology | 1995 | Control group not matched for age/education |
| Silvoni | Frontiers in Neuroscience | 2009 | Control group not matched for age/education |
| Tsujimoto | Journal of the Neurological Sciences | 2011 | Control group not matched for age/education |
| York | Journal of Neurology | 2014 | Control group not matched for age/education |
| Cobble | Journal of the Neurological Sciences | 1998 | Did not meet WFN El Escorial criteria |
| Frank | Clinical Neurology & Neurosurgery | 1997 | Did not meet WFN El Escorial criteria |
| Hartikainen | Journal of Neural Transmission | 1993 | Did not meet WFN El Escorial criteria |
| Iwasaki | International Journal of Neuroscience | 1990 | Did not meet WFN El Escorial criteria |
| Iwasaki | Acta Neurologica Scandinavica | 1990 | Did not meet WFN El Escorial criteria |
| Poloni | Acta Neurologica Scandinavica | 1986 | Did not meet WFN El Escorial criteria |
| Abrahams | Journal of the Neurological Sciences | 1995 | Effect size calculation not possible |
| Amato | Frontiers in Aging Neuroscience | 2013 | Effect size calculation not possible |
| Cerami | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2014 | Effect size calculation not possible |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Chari | Neuropsychologia | 1996 | Effect size calculation not possible |
| Consonni | Behavioural Neurology | 2013 | Effect size calculation not possible |
| Crespi | Cortex | 2014 | Effect size calculation not possible |
| Elamin | Neurology | 2013 | Effect size calculation not possible |
| Flaherty-Craig | Neurology | 2006 | Effect size calculation not possible |
| Flaherty-Craig | Cognitive & Behavioral Neurology | 2011 | Effect size calculation not possible |
| Ji | BMC Neurology | 2012 | Effect size calculation not possible |
| Lillo | Amyotrophic Lateral Sclerosis | 2012 | Effect size calculation not possible |
| Moretti | Dementia & Geriatric Cognitive Disorders | 2002 | Effect size calculation not possible |
| Moretti | Archives of Gerontology and Geriatrics | 2001 | Effect size calculation not possible |
| Murphy | Amyotrophic Lateral Sclerosis | 2012 | Effect size calculation not possible |
| Papeo | Cortex | 2015 | Effect size calculation not possible |
| Pekkonen | Clinical Neurophysiology | 2004 | Effect size calculation not possible |
| Pinkhardt | BMC Neurolgy | 2006 | Effect size calculation not possible |
| Reverberi | Cortex | 2014 | Effect size calculation not possible |
| Rippon | Archives of Neurology | 2006 | Effect size calculation not possible |
| Robinson | Journal of Neurology | 2006 | Effect size calculation not possible |
| Steenland | Neuroepidemiology | 2010 | Effect size calculation not possible |
| Strong | Neurology | 1999 | Effect size calculation not possible |
| Stukovnik | Journal of Clinical & Experimental Neuropsychology | 2010 | Effect size calculation not possible |
| Wicks | Journal of Neurology | 2009 | Effect size calculation not possible |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Yuan | International Journal of Neuroscience | 2010 | Effect size calculation not possible |
| Zaehle | PLoS ONE | 2013 | Effect size calculation not possible |
| Agosta | Neurobiology of Aging | 2014 | MND patients included in patient group |
| Ahlskog | Neurology | 1998 | MND patients included in patient group |
| Canu | PLoS ONE | 2013 | MND patients included in patient group |
| Capitani | Schweizer Archiv fur Neurologie und Psychiatrie | 1994 | MND patients included in patient group |
| Dary-Auriol | Revue Neurologique | 1997 | MND patients included in patient group |
| Palmieri | Journal of the Neurological Sciences | 2009 | MND patients included in patient group |
| Talbot | Journal of Neurology | 1995 | MND patients included in patient group |
| Wicks | Neurology | 2006 | MND patients included in patient group |
| Abe | Journal of Neuroimaging | 1997 | No (standardised) neuropsychological tests |
| Abrahams | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2014 | No (standardised) neuropsychological tests |
| Achi | Neurology Research International | 2012 | No (standardised) neuropsychological tests |
| Agosta | PLoS ONE | 2012 | No (standardised) neuropsychological tests |
| Andersen | The Lancet Neurology | 2012 | No (standardised) neuropsychological tests |
| Anderson | Journal of the Neurological Sciences | 1995 | No (standardised) neuropsychological tests |
| Aronson | Journal of Speech & Hearing Disorders | 1968 | No (standardised) neuropsychological tests |
| Bak | Rinsho Shinkeigaku - Clinical Neurology | 2010 | No (standardised) neuropsychological tests |
| Bak | Brain and Language | 2004 | No (standardised) neuropsychological tests |
| Bede | Journal of Neurology, Neurosurgery and Psychiatry | 2013 | No (standardised) neuropsychological tests |
| Belzil | European Journal of Human Genetics | 2013 | No (standardised) neuropsychological tests |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Ben Bashat | Amyotrophic Lateral Sclerosis | 2011 | No (standardised) neuropsychological tests |
| Bizovicar | Clinical Neurology and Neurosurgery | 2012 | No (standardised) neuropsychological tests |
| Campbell | Journal of the Neurological Sciences | 1984 | No (standardised) neuropsychological tests |
| Cardenas-Blanco | Journal of Neurology | 2014 | No (standardised) neuropsychological tests |
| Caruso | Journal of Speech & Hearing Research | 1987 | No (standardised) neuropsychological tests |
| Cistaro | European Journal of Nuclear Medicine and Molecular Imaging | 2014 | No (standardised) neuropsychological tests |
| Conforti | Journal of Neurology, Neurosurgery and Psychiatry | 2011 | No (standardised) neuropsychological tests |
| Czell | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2013 | No (standardised) neuropsychological tests |
| Filippini | Neurology | 2010 | No (standardised) neuropsychological tests |
| Flaherty-Craig | Neurodegenerative Disease Management | 2011 | No (standardised) neuropsychological tests |
| Floris | Amyotrophic Lateral Sclerosis | 2012 | No (standardised) neuropsychological tests |
| Goldstein | The Lancet Neurology | 2013 | No (standardised) neuropsychological tests |
| Goldstein | Journal of Neurology | 2011 | No (standardised) neuropsychological tests |
| Guo | European Journal of Neurology | 2014 | No (standardised) neuropsychological tests |
| Josephs | Neurology | 2007 | No (standardised) neuropsychological tests |
| Kasahara | BMC Neuroscience | 2012 | No (standardised) neuropsychological tests |
| Kent | Journal of Speech & Hearing Research | 1992 | No (standardised) neuropsychological tests |
| Kew | Brain | 1993 | No (standardised) neuropsychological tests |
| Khedr | Neurophysiologie Clinique | 2011 | No (standardised) neuropsychological tests |
| Kiernan | Brain | 1994 | No (standardised) neuropsychological tests |
| Konrad | Experimental Brain Research | 2006 | No (standardised) neuropsychological tests |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Kwan | PLoS ONE | 2012 | No (standardised) neuropsychological tests |
| Lillo | PLoS ONE | 2012 | No (standardised) neuropsychological tests |
| Lomen-Hoerth | Dementia & Geriatric Cognitive Disorders | 2004 | No (standardised) neuropsychological tests |
| Lulé | Neurorehabilitation and Neural Repair | 2007 | No (standardised) neuropsychological tests |
| Lulé | Journal of Neurology | 2013 | No (standardised) neuropsychological tests |
| Ma | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2014 | No (standardised) neuropsychological tests |
| Maekawa | Brain | 2004 | No (standardised) neuropsychological tests |
| Munte | Acta Neurologica Scandinavica | 1998 | No (standardised) neuropsychological tests |
| Munte | Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders | 1999 | No (standardised) neuropsychological tests |
| Neary | Journal of Neurology, Neurosurgery and Psychiatry | 2013 | No (standardised) neuropsychological tests |
| Oketa | Acta Neurologica Scandinavica | 2013 | No (standardised) neuropsychological tests |
| Patacchioli | Journal of Endocrinological Investigation | 2003 | No (standardised) neuropsychological tests |
| Pohl | Archives of Neurology | 2001 | No (standardised) neuropsychological tests |
| Poloni | Italian Journal of Neurological Sciences | 1986 | No (standardised) neuropsychological tests |
| Ratti | Neurobiology of Aging | 2012 | No (standardised) neuropsychological tests |
| Sage | Human Brain Mapping | 2009 | No (standardised) neuropsychological tests |
| Santhosh | Cognitive Brain Research | 2004 | No (standardised) neuropsychological tests |
| Sato | Neuroradiology | 2010 | No (standardised) neuropsychological tests |
| Semenza | Frontiers in Aging Neuroscience | 2014 | No (standardised) neuropsychological tests |
| Stanton | Journal of Neurology | 2007 | No (standardised) neuropsychological tests |
| Tan | PLoS ONE | 2014 | No (standardised) neuropsychological tests |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Tanaka | Neurological Research | 2003 | No (standardised) neuropsychological tests |
| Tessitore | Brain Research Bulletin | 2006 | No (standardised) neuropsychological tests |
| Turner | Brain | 2005 | No (standardised) neuropsychological tests |
| Woolley | Amyotrophic Lateral Sclerosis | 2010 | No (standardised) neuropsychological tests |
| Abe | Journal of the Neurological Sciences | 1996 | No statement about exclusion of demented patients |
| Barbagallo | Neurological Sciences | 2014 | No statement about exclusion of demented patients |
| Gil | Archives of Neurology | 1995 | No statement about exclusion of demented patients |
| Abrahams | Journal of Neurology | 2005 | Patient selection based on performance |
| Abrahams | Brain | 1996 | Patient selection based on performance |
| Passamonti | Neurobiology of Aging | 2013 | Patient selection based on performance |
| Dombroski | JAMA Neurology | 2013 | Patients with ALS plus syndromes were included |
| Abrahams | Journal of the Neurological Sciences | 1995 | Same patient group as Abrahams 1997 |
| Abrahams | Neurology | 2005 | Same patient group as Abrahams 2004 |
| Agosta | Neurobiology of Aging | 2013 | Same patient group as Sarro 2011 |
| Gallassi | Acta Neurologica Scandinavica | 1985 | Same patient group as Gallassi 1989 |
| Raaphorst | Neurology | 2014 | Same patient group as Raaphorst 2011 |
| Abe | Neurology | 1993 | Uncontrolled study |
| Ahn | Canadian Journal of Neurological Sciences | 2011 | Uncontrolled study |
| Barson | Journal of the Neurological Sciences | 2000 | Uncontrolled study |
| Bartels | Neuromuscular Disorders | 2008 | Uncontrolled study |
| Bede | Neurology | 2013 | Uncontrolled study |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Bede | Neurology | 2013 | Uncontrolled study |
| Bensch | Journal of Neural Engineering | 2014 | Uncontrolled study |
| Burrell | Brain | 2011 | Uncontrolled study |
| Byrne | The Lancet Neurology | 2012 | Uncontrolled study |
| Chang | Neurology | 2005 | Uncontrolled study |
| Chio | Archives of Neurology | 2010 | Uncontrolled study |
| Christidi | Brain Imaging and Behaviour | 2013 | Uncontrolled study |
| Cistaro | European Journal of Nuclear Medicine and Molecular Imaging | 2012 | Uncontrolled study |
| Di Paolo | Revista Portuguesa de Pneumologia | 2013 | Uncontrolled study |
| Duning | PLoS ONE | 2011 | Uncontrolled study |
| Elamin | Neurology | 2011 | Uncontrolled study |
| Flaherty-Craig | Amyotrophic Lateral Sclerosis | 2009 | Uncontrolled study |
| Gordon | Amyotrophic Lateral Sclerosis | 2011 | Uncontrolled study |
| Gordon | Amyotrophic Lateral Sclerosis | 2010 | Uncontrolled study |
| Gordon | Amyotrophic Lateral Sclerosis | 2007 | Uncontrolled study |
| Grace | Canadian Journal of Neurological Sciences | 2011 | Uncontrolled study |
| Hicks | PLoS ONE | 2013 | Uncontrolled study |
| Ichikawa | European Neurology | 2013 | Uncontrolled study |
| Keil | BMC Neuroscience | 2012 | Uncontrolled study |
| Korner | BMC Neurology | 2013 | Uncontrolled study |
| Kwan | NeuroImage: Clinical | 2013 | Uncontrolled study |
| Mantovan | European Journal of Neurology | 2003 | Uncontrolled study |

**Table S2.** Continued.

| Author | Journal | Year | Reason for exclusion |
|---|---|---|---|
| Martin | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2014 | Uncontrolled study |
| Meoded | Dementia and Geriatric Cognitive Disorders | 2013 | Uncontrolled study |
| Mioshi | Neurology | 2014 | Uncontrolled study |
| Mioshi | Neurology | 2013 | Uncontrolled study |
| Muller | Journal of Neuroimaging | 2011 | Uncontrolled study |
| Oh | PLoS ONE | 2014 | Uncontrolled study |
| Ohnishi | Journal of Nuclear Medicine | 1995 | Uncontrolled study |
| Raaphorst | Neurology | 2012 | Uncontrolled study |
| Rajeswaran | Neuropsychological Trends | 2013 | Uncontrolled study |
| Schreiber | Journal of Neurology | 2005 | Uncontrolled study |
| Schuster | Neurobiology of Aging | 2014 | Uncontrolled study |
| Smith | Amyotrophic Lateral Sclerosis & Other Motor Neuron Disorders | 2004 | Uncontrolled study |
| Snowden | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2013 | Uncontrolled study |
| Stoppel | NeuroImage Clinical | 2014 | Uncontrolled study |
| Tremolizzo | Journal of Neurology | 2014 | Uncontrolled study |
| Trojsi | Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration | 2013 | Uncontrolled study |
| Waldemar | Journal of the Neurological Sciences | 1992 | Uncontrolled study |
| Wilson | Neurology | 2001 | Uncontrolled study |
| Wei | Journal of Neurology | 2014 | Uncontrolled study |
| Witiuk | Journal of Neuroscience | 2014 | Uncontrolled study |
| Yamauchi | Journal of the Neurological Sciences | 1995 | Uncontrolled study |

Legend. See the inclusion criteria for details on reasons for exclusion. WNF El Escorial criteria: World Federation of Neurology El Escorial criteria

**Table S3.** Adjustments for motor disabilities and/or dysarthria

| | | Study ID |
|---|---|---|
| Correction for dysarthria and motor disabilities | Adjusted neuropsychological battery | 1, 8, 12, 13, 19, 20, 21, 22, 31, 35, 36, 39, 40, 43, 44 |
| | Exclusion of patients with severe dysarthria or motor disabilities | 2, 3, 4, 9, 10, 14, 15, 16, 17, 18, 19, 23, 24, 27, 28, 29, 30.1, 30.2, 32, 33, 34, 38, 39, 41, 42 |
| | Not all patients performed all tests | 5, 6, 7, 11, 25, 26, 39 |
| Correction for respiratory dysfunction | Inclusion criteria FVC >70% | 12, 14, 25, 28, 31, 33, 39, 43 |
| | Blood gas analysis | 3, 35 |
| | Statement of authors: no severe respiratory dysfunction | 8, 17, 18, 20, 23, 24, 27, 29, 30.1, 30.2, 38 |
| | No information | 1, 2, 4, 5, 6, 7, 9, 10, 11, 13, 15, 16, 19, 21, 22, 26, 32, 34, 36, 37, 40, 41, 42, 44 |
| Depression and anxiety | More depressive/anxiety symptoms than healthy volunteers | 7, 10, 16, 20, 27, 39 |
| | Depressive/anxiety symptoms comparable to healthy volunteers | 3, 5, 8, 9, 12, 14, 21, 23, 24, 26, 28, 29, 30.2, 33, 34, 35 |
| | No information | 1, 2, 4, 6, 11, 13, 15, 17, 18, 19, 22, 25, 30.1, 31, 32, 36, 37, 38, 40, 41, 42, 43, 44 |
| Psychoactive medication use | Exclusion criterion | 2, 4, 5, 7, 10, 12, 14, 16, 20, 21, 23, 26, 28, 31, 32, 33, 35, 37, 38, 39, 44 |
| | No exclusion criterion | 13 |
| | No information | 1, 3, 6, 8, 9, 11, 15, 17, 18, 19, 22, 24, 25, 27, 29, 30.1, 30.2, 34, 36, 40, 41, 42, 43 |

Legend. Study ID corresponds to the study ID in Table 1.







**Table S4.** References of included studies


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**Table S5.** Neuropsychological tests used for the assessment of the cognitive domains

| Cognitive domain | Neuropsychological tests | K |
|---|---|---|
| Visuoconstructive functions | WAIS block design | 3 |
| | Rey complex figure, copy | 1 |
| | Copy design | 1 |
| MMSE | Mini Mental State Examination | 17 |
| Fluency | Letter fluency | 23 |
| | Category fluency | 15 |
| | Design fluency | 4 |
| | Alternating fluency | 1 |
| Language | Boston naming test | 9 |
| | McKenna Graded naming test | 6 |
| | Simple and complex analogies | 2 |
| | Peabody picture vocabulary test | 1 |
| | Phrase construction | 1 |
| | Picture naming | 1 |
| | Action naming test | 1 |
| | Arizona battery for communication disorders | 1 |
| | Western Aphasia Battery | 1 |
| | Cookie Theft picture | 1 |
| | British Picture Vocabulary scale | 1 |
| | Test for Reception of Grammar | 1 |
| | Category Specific Names test | 1 |
| | Oral and written naming of nouns | 1 |
| | Judgements of synonyms | 1 |
| | Assessment of language processing in aphasia | 1 |
| | Graded difficulty spelling test | 1 |
| | Pyramids and Palm Trees test | 1 |
| | Kissing and Dancing test | 1 |
| | Spot the Word test | 1 |
| | Token test | 1 |
| Social cognition | The awareness of social interference test | 2 |
| | Ekman faces test | 1 |
| | Reading the mind in the eyes | 1 |
| | Faux pas Task | 1 |
| | Aprosodia Battery | 1 |
| | Judgement of preference task | 1 |
| | Ekman caricatures test | 1 |
| Delayed verbal memory | Auditory verbal learning test | 8 |
| | California verbal learning test | 3 |
| | Prose memory test | 3 |
| | Delayed recognition task | 1 |
| | Wechsler memory scale | 1 |
| | Hopkins verbal learning task | 1 |
| | Brierly-Medford sentences | 1 |
| | Phelps words task | 1 |
| | Rivermead Behavioral Memory Test | 1 |
| | Logical memory | 1 |





**Table S5.** Continued.

| Cognitive domain | Neuropsychological tests | K |
|---|---|---|
| Psychomotor speed | Trail making test, part A | 8 |
| | Stroop test, part A and B | 6 |
| | Symbol digit modalities test | 6 |
| | Barrage test (time to complete) | 1 |
| | Kendrick Digit Copying Test | 1 |
| | Simple reaction time (Test for Attentional Performance) | 1 |
| Immediate verbal memory | Auditory verbal learning test | 5 |
| | Recognition memory test | 3 |
| | California verbal learning test | 3 |
| | Prose memory test | 2 |
| | Serial digit learning test | 1 |
| | Paired associate learning | 1 |
| | Conditional associative learning task | 1 |
| | Hopkins verbal learning task | 1 |
| | Verbal learning test | 1 |
| | Wechsler memory scale | 1 |
| | Brow-Peterson Interference Test | 1 |
| | Rivermead Behavioral memory test | 1 |
| | Logical memory | 1 |
| | Words recognition memory test | 1 |
| Executive function | Wisconsin Card Sorting test | 16 |
| | Stroop test | 14 |
| | Trail making test (part B-A) | 10 |
| | Brixton Spatial Anticipation Test | 5 |
| | Hayling Sentence Completion Test | 3 |
| | Go/NoGo (test of attentional performance) | 1 |
| | Weigl block task | 1 |
| | Holiday Apartment test | 1 |
| | Probabilistic reversal learning test | 1 |
| | One-touch Stockings of Cambridge | 1 |
| | Card Sorting test (Delis-Kaplan Executive Function System) | 1 |
| | Iowa gambling test | 1 |
| | Tower of Hanoi | 1 |
| Attention | Digit span | 11 |
| | Corsi Block tapping test | 3 |
| | Paced Auditory Serial Addition test | 2 |
| | Counting task | 1 |
| | Continuous performance test | 1 |
| | Letter Span | 1 |
| | Visual Search and Attention Test | 1 |
| | Letter number sequencing | 1 |
| | WAIS arithmetic | 1 |
| | Number processing and calculation battery | 1 |

**Table S5.** Continued.

| Cognitive domain | Neuropsychological tests | K |
|---|---|---|
| Verbal IQ | WAIS | 8 |
| | Mill Hill Vocabulary scale | 1 |
| | Mehrfachwahl-Wortenschatz-Intelligenztest | 1 |
| Visual memory | Kendrick Object Learning Test | 4 |
| | Rey complex figure, delayed recall | 3 |
| | Doors test | 3 |
| | Recognition Memory Test | 2 |
| | Benton facial recognition test | 2 |
| | Non-verbal Learning Test | 1 |
| | Immediate visual memory test | 1 |
| | Picture recall and recognition test | 1 |
| | Conditional associative learning test | 1 |
| Visuoperceptive functions | Judgement of Line Orientation test | 4 |
| | Visual Object and Space Perception Battery | 3 |
| | Barrage Test | 1 |
| | Little Men Test | 1 |
| | Money Road map | 1 |
| | Fragmented figures | 1 |
| | Differential Aptitude Test | 1 |
| | Hand laterality task | 1 |
| | Mirror letter discrimination task | 1 |
| | Mental rotation test | 1 |

Legend. k: number of studies that administered the neuropsychological test.

# 3

## The cognitive profile of behavioural variant FTD and its similarities with ALS: a systematic review and meta-analysis

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## ABSTRACT

Approximately 30% of patients with amyotrophic lateral sclerosis (ALS) have cognitive impairment and 8-14% fulfil the criteria for behavioural variant frontotemporal dementia (bvFTD). The cognitive profiles of ALS and bvFTD have been reported to be comparable, but this has never been systematically investigated. We aimed to determine the cognitive profile of bvFTD and examine its similarities with that of ALS, to provide evidence for the existence of a cognitive disease continuum encompassing bvFTD and ALS. We therefore systematically reviewed neuropsychological studies on patients with bvFTD and healthy volunteers. Neuropsychological tests were divided in 10 cognitive domains and effect sizes were calculated for all domains and compared with the cognitive profile of ALS by means of a visual comparison and a Pearson's *r* correlation coefficient. We included 120 studies, totalling 2425 patients with bvFTD and 2798 healthy controls. All cognitive domains showed substantial effect sizes, indicating cognitive impairment in bvFTD patients compared to healthy controls. The cognitive domains with the largest effect sizes were social cognition, verbal memory and fluency (1.77 – 1.53). The cognitive profiles of bvFTD and ALS (10 cognitive domains, 1287 patients) showed similarities on visual comparison and a moderate correlation 0.58 (p=0.13). When social cognition, verbal memory, fluency, executive functions, language and visuoperception were considered, i.e. the cognitive profile of ALS, Pearson's *r* was 0.73 (p=0.09), which raised to 0.92 (p=0.03), when language was excluded in this systematic analysis of patients with a non-language subtype of FTD. The cognitive profile of bvFTD consists of deficits in social cognition, verbal memory, fluency and executive functions and shows similarities with the cognitive profile of ALS. These findings support a cognitive continuum encompassing ALS and bvFTD.








## INTRODUCTION

Eight to 14 per cent of patients with amyotrophic lateral sclerosis (ALS) have concurrent behavioural variant frontotemporal dementia (bvFTD) and up to 30 per cent of patients with ALS are reported to have mild to moderate cognitive impairment.[1-3] The mild cognitive deficits of ALS are attributed to frontotemporal dysfunction, because they include executive, memory and language deficits and impairment of social cognition.[1, 4-6] These findings, in combination with brain imaging abnormalities and pathological changes in the frontotemporal lobes of patients with ALS and pathogenic mutations associated with both diseases, have contributed to the hypothesis that ALS and (bv)FTD are part of a disease continuum.[6, 7]

The existence of this disease continuum would be strengthened by observations that mild cognitive deficits progress to bvFTD in a proportion of patients with ALS. Although progressive paralysis complicates the performance of longitudinal studies in ALS, existing neuropsychological data, albeit sparse and including a limited number of patients with ALS, have failed to show progression of cognitive deficits.[8, 9] Another observation that questions the presence of a disease continuum between ALS and bvFTD on the basis of cognition, is a discrepancy between the cognitive criterion of the international consensus criteria of bvFTD, and the cognitive profile of ALS. The bvFTD diagnostic criteria include relative sparing of memory and visuospatial functions, while these two cognitive domains, in particular memory, are not spared in patients with ALS, according to recent studies.[10-15]

Many neuropsychological studies have been performed in patients with bvFTD, suggesting a cognitive profile including executive and social cognition deficits, with relative sparing of memory and visuospatial skills.[10] A meta-analysis of these neuropsychological studies in bvFTD could reveal new insights in the cognitive profile of bvFTD, similar to our finding that the cognitive deficits of ALS are more extensive than previously thought.[13] Secondly, such a meta-analysis in bvFTD enables a comparison with the cognitive profile of ALS, which may increase our understanding of the nature and extent of brain involvement in these disorders.

Therefore, the aim of the current study was to define the cognitive profile of bvFTD and to examine similarities with ALS. We performed a systematic review and meta-analysis of neuropsychological studies in patients with bvFTD and healthy volunteers, and compared the results to our previous meta-analysis of the cognitive profile of patients with ALS.[13]

## METHODS

### Literature search

Medline (1966-2017), Embase (1970-2017) and PsycInfo (1970-2017) were searched on November 29th 2017 for neuropsychological studies of patients with bvFTD, written in English, German, French or Dutch. Two authors screened all abstracts and evaluated full-text articles (EB and MKT for the original search in 2014, EB and RG for the updated search). References of articles were also screened and considered for inclusion. Keywords included frontotemporal dementia (FTD) and its synonyms, cognition and a selection of neuropsychological tests (supplementary table e-1). Amyotrophic lateral sclerosis (ALS) and its synonyms were also included as key words, due to its association with FTD.

### Study selection

All studies had to meet the following criteria:

- Inclusion of a control group of healthy subjects.
- Patients had to be diagnosed with bvFTD according to validated clinical criteria (Neary or Rascovsky criteria).[10, 16] Patients with other forms of frontotemporal lobar degeneration (FTLD) were excluded (i.e. patients with semantic dementia or progressive non-fluent aphasia). When these patients were also studied, data of patients with bvFTD had to be reported separately, in order to allow extraction of their data. When patients with ALS or ALS-FTD were included, their data had to be reported separately.
- Age and education matched controls had to be included or, when controls were not matched, norm scores corrected for age and education had to be used (i.e. T-score, z-score).
- Data of at least one validated neuropsychological test had to be reported. When studies had only performed the mini mental state examination (MMSE), dementia screening tests and/or IQ tests, they were not included. In order to allow conversion to effect sizes, the mean and SD of raw test scores, T-scores or z-scores for patients and controls had to be reported.
- Studies had to report unique cohorts. If papers had reported data of the same cohort, the study with the largest sample was included.

With the exception of patients with other forms of FTLD, there were no other exclusion criteria.

### Data extraction

We extracted the following demographic and clinical variables from the articles: age (years), disease duration (months), educational level (years of formal education), disease severity (measured with validated dementia rating scales or, when these were not available, with results of dementia screening tests), use of psychoactive medication and depressive/anxiety symptoms.

We categorized all neuropsychological tests in 10 cognitive domains: social cognition, verbal memory, fluency, executive functions, visual memory, language, attention, visuoperception, psychomotor speed and visuoconstruction. A description of each cognitive domain and the included neuropsychological tests can be found in supplementary table e-2. We extracted all the neuropsychological test scores, i.e. the mean, standard deviation and number of participants of both the patient and control group. To reduce extraction errors, data extraction was performed by two authors and differences were resolved by consensus (EB, MKT).[17]

### Subgroup analyses

Subgroup analyses were performed to find explanations for moderate or substantial heterogeneity in the cognitive domains. The following demographic and clinical variables were assessed in the subgroup analyses, based on a median split: age (years), educational level (years of formal education), disease duration (years) and disease severity (dementia rating scale; i.e. Clinical Dementia Rating scale (CDR and CDR sum of boxes), Addenbrooke's Cognitive Evaluation – revised (ACE-R) and the Mattis Dementia Rating Scale (MDRS)).

### Statistical analysis

Demographic and clinical variables of the bvFTD meta-analysis and ALS meta-analysis were summarized using simple descriptive statistics. When a study had presented longitudinal data, only data from the first visit was used for analysis. Effect sizes were expressed as Hedges' g, i.e. mean difference between patients with FTD and healthy controls, divided by the pooled SD and calculated in Review Manager.[18] First, we divided all cognitive tests per study in the before-mentioned cognitive domains. Then, we calculated the effect sizes for all cognitive domains per study. When studies had reported data of more than one test within a specific cognitive domain, an averaged effect size was calculated, resulting in only one effect size per study in each cognitive domain. A random effects model was used to pool all effect sizes in each cognitive domain. A positive effect size indicated impairment of patients with FTD, compared to healthy controls. Effect sizes were considered small when < 0.5, moderate when between 0.5 and 0.8 and large when > 0.8.[19] Statistical heterogeneity among studies was assessed with the Cochran's Q test ($c^2$) and the $I^2$ statistic. The $c^2$ test measures if differences in the results are compatible with chance alone. The $I^2$ statistic is an estimate of the percentage of the variation across studies that

is due to heterogeneity rather than chance. $I^2$ cut-off points for low, moderate and substantial heterogeneity were 25%, 50% and 75%, respectively.[20]

To assess the impairment of patients with bvFTD on specific neuropsychological tests and to explore heterogeneity, effect sizes of individual tests were calculated. This was performed for all tests that were administered in 3 or more studies. Statistical uncertainty was expressed in a 95% CI. We used IBM Statistics SPSS (V.20) and Review Manager (V.5.3) for the statistical analyses.[18]

**Comparison of the cognitive profiles of bvFTD and ALS**

The effect sizes of the bvFTD meta-analysis were compared with the effect sizes of our updated meta-analysis of the cognitive profile of ALS, encompassing 1287 patients and 10 cognitive domains.[13] We expected to find some differences between the effect sizes of the bvFTD and ALS meta-analyses. Due to exclusion of patients with dementia in the ALS meta-analysis, we expected the effect sizes of the bvFTD meta-analysis to be systematically larger. However, we assumed that the effect size of language would be relatively larger in the ALS meta-analysis, because in the current meta-analysis on bvFTD, patients with language variants of FTLD were excluded.

We compared the bvFTD and ALS effect sizes in two different manners: a visual comparison and a comparison using correlation coefficients.

First, we depicted the effect sizes for each cognitive domain of both disorders into a graph and visually compared the sizes and directions of the effect sizes between bvFTD and ALS. If the cognitive profiles would be similar, a comparable pattern would emerge: for example a higher effect size for the executive domain compared to the verbal memory domain in both disorders.

Second, we used correlation coefficients to assess the association between the effect sizes of bvFTD and ALS. We calculated three Pearson's *r*s; the first included all cognitive domains except the domains with bias due to motor impairment (i.e. psychomotor speed and visuoconstruction); the second included all, so-called ALS-specific cognitive domains, and the third included all ALS-specific cognitive domains except language. The latter was done because we expected a difference between the bvFTD and ALS effect size of this domain, given our exclusion criterion (patients with other forms of FTLD, i.e. semantic dementia and progressive non-fluent aphasia were excluded). The ALS-specific domains were chosen based on recent literature of neuropsychological deficits in patients with ALS.[13, 21] Accordingly, the domains social cognition, verbal memory, fluency, executive functions, language and visuoperception were





considered ALS-specific. The latter domain is included in the ALS-specific domains because it is typically spared in ALS.[13]

**Risk of bias**

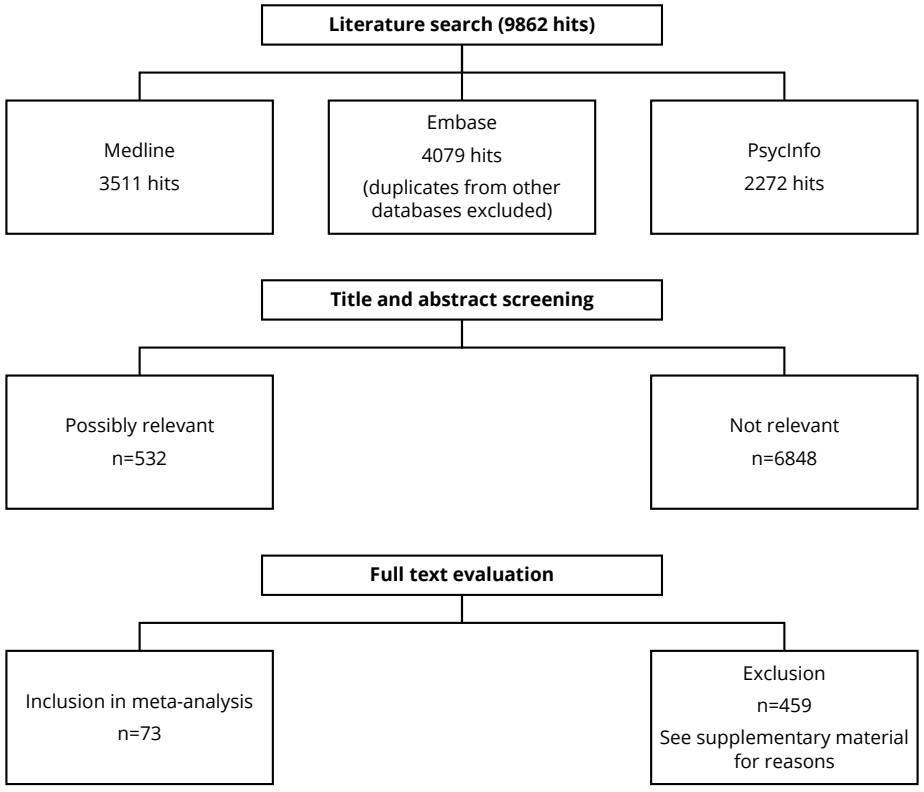
We assessed the quality of included articles with the Newcastle - Ottawa quality assessment scale (maximum score 8 points, higher scores indicating better quality).[13, 22]

We investigated the probability of a relevant publication bias in all cognitive domains with the fail-safe N, which was calculated with Rosenberg's fail-safe number calculator.[23, 24] This represents the number of studies without an effect that would need to be added to the meta-analysis to obtain a non-significant pooled effect size, i.e. $p > 0.05$. We also calculated the tolerance level, as a benchmark to assess the observed fail-safe N ($5 \times$ number of studies + 10). If the fail-safe N is large in comparison to the tolerance level, the observed result is considered to be a reliable estimate of the real effect.

## RESULTS

The literature search resulted in 9862 hits, of which 848 articles underwent full-text evaluation (figure 1). One hundred and twenty articles were included in the meta-analysis and their characteristics are shown in supplementary table e-3. The reasons for exclusion of the remaining 728 articles can be found in the supplementary material (supplementary table e-4).

**Figure 1.** Flowchart of literature search and study selection




### Study characteristics

A total of 2425 patients with bvFTD (64.6% male) and 2798 healthy volunteers were included in the meta-analysis. The mean (SD) age and educational level of the patients was 64.1 (3.4) years and 12.8 (2.7) years, respectively. Disease duration was reported in a limited number of studies (n=62, 51.2%), with a median (range) of 4.2 (1.0 – 9.2) years. Disease severity, measured with the CDR and CDR sum of boxes, ACE-R and MDRS, was reported in 65 studies (54.2%) and was moderate in most patients (supplementary table e-3).[25-27] The patients included in the bvFTD and ALS meta-analyses had approximately the same mean age, educational level and sex distribution (table 1). The median MMSE was lower in the bvFTD meta-analysis (25.3, range 19.6-28.3) compared to the ALS meta-analysis (28.0, range 25.7-29.0).





**Table 1.** Demographic, disease and study variables of bvFTD and ALS meta-analyses

| | bvFTD meta-analysis | ALS meta-analysis[9] |
|---|---|---|
| Studies (N) | 120 | 44 |
| Patients (N) | 2425 | 1287 |
| Sex (male %) | 64.6% | 62.8% |
| Age (years) | 64.1 (3.4) | 59.2 (3.9) |
| Educational level (years) | 12.7 (2.7) | 11.7 (2.3) |
| Disease duration (years) | 4.2 (1 – 9.2) | 2.0 (0.7 – 6.7) |
| MMSE score | 25.3 (19.6 – 28.3) | 28.0 (25.7 – 29.0) |
| Neuropsychological tests per study | 6 (1 – 30) | 8 (1 – 30) |

Legend. Numbers are presented as mean (standard deviation) or median (range) when appropriate.

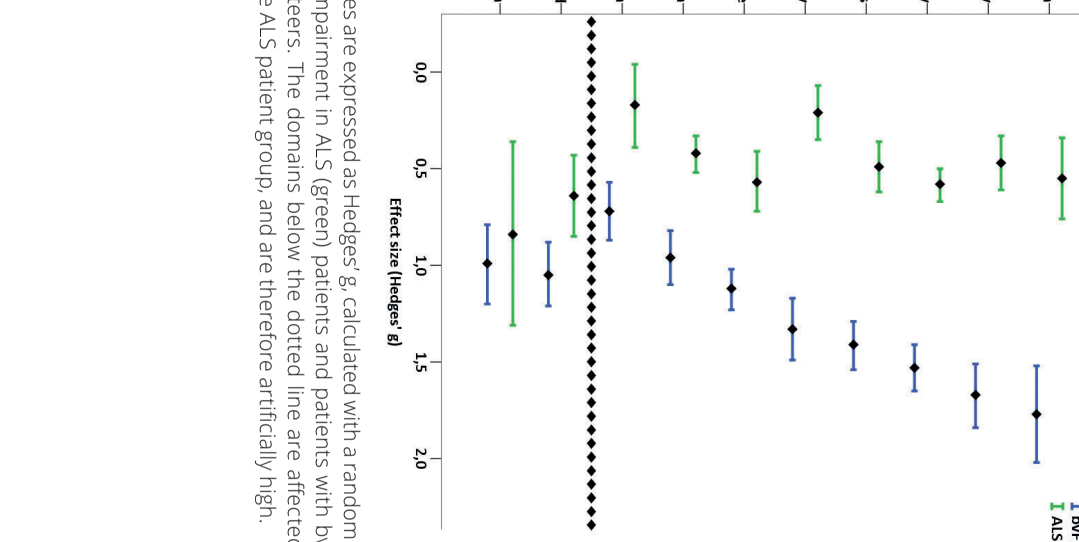


### Effect sizes of cognitive domains

All cognitive domains showed substantial pooled effect sizes, i.e. impairment of patients with bvFTD compared to healthy volunteers. The three largest effect sizes were found for the domains social cognition (1.77), verbal memory (1.67) and fluency (1.53) (figure 2 and table 2).

For all cognitive domains pooled effect sizes of individual tests within the domains were calculated (table 2). The three largest effect sizes were found for the recognition memory test – words (2.31; verbal memory), Hayling test (2.19; executive function), the awareness of social inference test (1.96; social cognition) and Faux pas test (1.96; social cognition).

**Figure 2.** Comparison of the pooled effect sizes of the cognitive domains in bvFTD and ALS




Legend. Effect sizes are expressed as Hedges' g, calculated with a random effects model. Positive values indicate impairment in ALS (green) patients and patients with bvFTD (blue), compared to healthy volunteers. The domains below the dotted line are affected by bias do to motor impairment in the ALS patient group, and are therefore artificially high.

**Table 2.** Pooled effect sizes* and heterogeneity statistics of all cognitive domains and a selection of neuropsychological tests

| Cognitive domain | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ | Fail-safe N | Tolerance level |
|---|---|---|---|---|---|---|---|---|---|
| **Social cognition** | **1.77** | **1.52-2.02** | **40** | **1636** | **258.92** | **$< 10^{-5}$** | **85%** | **5514** | **210** |
| Ekman test | 1.89 | 1.46-2.31 | 16 | 671 | 89.18 | $< 10^{-5}$ | 83% | | |
| RME | 1.39 | 0.90-1.88 | 11 | 429 | 46.44 | $< 10^{-5}$ | 78% | | |
| TASIT | 1.96 | 1.72-2.20 | 10 | 426 | 11.53 | 0.24 | 22% | | |
| FPT | 1.96 | 1.26-2.67 | 9 | 402 | 66.45 | $< 10^{-5}$ | 88% | | |
| ToM | 0.85 | 0.41-1.29 | 4 | 150 | 6.20 | 0.10 | 52% | | |
| **Verbal memory** | **1.67** | **1.51-1.84** | **55** | **2022** | **219.60** | **$< 10^{-5}$** | **75%** | **9455** | **285** |
| AVLT | 1.76 | 1.56-1.95 | 31 | 1130 | 68.02 | $< 10^{-4}$ | 56% | | |
| Logical memory | 0.84 | 0.55-1.13 | 8 | 250 | 18.26 | 0.01 | 62% | | |
| RMT words | 2.31 | 2.00-2.62 | 7 | 276 | 3.32 | 0.77 | 0% | | |
| FCSRT | 1.59 | 1.09-2.09 | 5 | 298 | 22.20 | 0.0002 | 82% | | |
| **Fluency** | **1.53** | **1.41-1.65** | **67** | **2743** | **125.49** | **$< 10^{-4}$** | **47%** | **11378** | **345** |
| Letter fluency | 1.68 | 1.51-1.84 | 58 | 2287 | 147.56 | $< 10^{-5}$ | 61% | | |
| Category fluency | 1.60 | 1.38-1.81 | 35 | 1400 | 97.71 | $< 10^{-5}$ | 65% | | |
| Design fluency | 1.48 | 1.16-1.79 | 6 | 306 | 3.19 | 0.67 | 0% | | |
| **Executive function** | **1.41** | **1.29-1.54** | **81** | **3238** | **260.52** | **$< 10^{-5}$** | **69%** | **14515** | **415** |
| TMT | 1.60 | 1.43-1.76 | 52 | 1959 | 133.19 | $< 10^{-5}$ | 62% | | |
| Stroop test | 1.18 | 0.92-1.43 | 23 | 827 | 76.97 | $< 10^{-5}$ | 71% | | |
| Hayling test | 2.19 | 1.87-2.51 | 23 | 1004 | 75.73 | $< 10^{-5}$ | 71% | | |
| WCST | 1.42 | 1.04-1.81 | 16 | 596 | 82.90 | $< 10^{-5}$ | 82% | | |
| IGT | 1.09 | 0.52-1.65 | 5 | 268 | 14.86 | 0.005 | 73% | | |
| Brixton test | 1.86 | 0.48-3.24 | 4 | 183 | 42.57 | $< 10^{-5}$ | 93% | | |
| **Visual memory** | **1.33** | **1.17-1.49** | **52** | **1823** | **155.47** | **$< 10^{-5}$** | **67%** | **5163** | **270** |
| RCF | 1.30 | 1.10-1.50 | 32 | 1168 | 80.19 | $< 10^{-5}$ | 61% | | |
| RMT faces | 1.53 | 1.13-1.94 | 11 | 379 | 27.26 | 0.002 | 63% | | |
| Doors test | 1.33 | 0.99-1.66 | 6 | 174 | 2.36 | 0.80 | 0% | | |

**Table 2.** Continued.

| Cognitive domain | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ | Fail-safe N | Tolerance level |
|---|---|---|---|---|---|---|---|---|---|
| **Language** | **1.12** | **1.02-1.23** | **57** | **2028** | **92.96** | **0.001** | **40%** | **4848** | **295** |
| BNT | 1.29 | 1.09-150 | 36 | 1344 | 97.91 | **$< 10^{-5}$** | 64% | | |
| SYDBAT | 1.43 | 1.25-1.62 | 10 | 292 | 9.47 | 0.40 | 5% | | |
| BPVS | 1.33 | 1.06-1.60 | 7 | 274 | 3.37 | 0.76 | 0% | | |
| Token test | 1.01 | 0.48-1.54 | 5 | 196 | 8.92 | 0.06 | 55% | | |
| PPTT | 0.81 | 0.43-1.19 | 4 | 132 | 1.14 | 0.77 | 0% | | |
| WAB | 0.81 | 0.34-1.29 | 4 | 77 | 1.64 | 0.65 | 0% | | |
| PPVT | 1.09 | 0.68-1.51 | 4 | 138 | 0.93 | 0.82 | 0% | | |
| **Psychomotor speed** | **1.05** | **0.88-1.21** | **39** | **1422** | **84.21** | **$< 10^{-4}$** | **55%** | **1663** | **205** |
| TMT A | 0.95 | 0.79-1.12 | 30 | 1075 | 44.50 | 0.03 | 35% | | |
| Stroop | 1.15 | 0.71-1.58 | 11 | 441 | 43.05 | $<10^{-5}$ | 77% | | |
| SDST | 1.53 | 0.87-2.19 | 3 | 112 | 3.97 | 0.14 | 50% | | |
| **Visuoconstruction** | **0.99** | **0.79-1.20** | **24** | **1004** | **46.56** | **0.003** | **51%** | **585** | **130** |
| RCF | 0.98 | 0.76-1.21 | **21** | 781 | 39.41 | 0.006 | 49% | | |
| **Attention** | **0.96** | **0.82-1.10** | **61** | **2454** | **243.84** | **$< 10^{-5}$** | **75%** | **4362** | **315** |
| Backward digit span | 0.99 | 0.82-1.15 | 54 | 2213 | 154.52 | $< 10^{-5}$ | 66% | | |
| Forward digit span | 0.72 | 0.55-0.88 | 38 | 1459 | 80.91 | $< 10^{-4}$ | 54% | | |
| Visual span | 0.72 | 0.32-1.12 | 7 | 279 | 19.44 | 0.003 | 69% | | |
| LNS | 1.66 | 1.21-2.11 | 3 | 115 | 2.01 | 0.37 | 0% | | |
| **Visuoperception** | **0.72** | **0.57-0.87** | **19** | **663** | **19.91** | **0.34** | **10%** | **232** | **105** |
| VOSP | 0.70 | 0.53-0.88 | 14 | 559 | 16.52 | 0.022 | 21% | | |
| JOLO | 0.94 | 0.53-1.36 | 5 | 104 | 1.97 | 0.74 | 0% | | |

Legend. Hedges' g: effect size, calculated with a random effects model; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p-value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q – degrees of freedom / Q x 100%); Fail-safe N: number of needed non-significant studies to obtain a non-significant effect size (p=0.05); Tolerance level: benchmark for the observed fail-safe N (estimated number of existing unpublished studies, 5k+10). Fail-safe N and tolerance level are not calculated for the effect sizes of the individual cognitive tests. RME: reading the mind in the eyes test; TASIT: the awareness of social inference test; FPT: faux pas test; ToM: theory of mind test; AVLT: auditory verbal learning test; RMT: recognition memory test; FCSRT: free and cued selective reminding test; TMT: trail making test; WCST: Wisconsin card sorting test; IGT: Iowa gambling test; RCF: Rey complex figure test; BNT: Boston naming test; SYDBAT: Sydney language battery; BPVS: British picture vocabulary scale; PPTT: pyramid and palm trees test; WAB: western aphasia battery; PPVT: Peabody picture vocabulary test; SDST: symbol digit substitution test; LNS: letter number sequencing; VOSP: visual object and space perception battery; JOLO: judgement of line orientation.

### Heterogeneity

There was moderate to substantial heterogeneity in the domains visuoconstruction, psychomotor speed, visual memory, executive functions, attention, verbal memory and social cognition ($I^2$ = 51-83%). Low to moderate heterogeneity was found for the domains language and fluency ($I^2$ = 40-47%). Relatively low heterogeneity was found in the domain visuoperception ($I^2$ = 10%).

### Subgroup analyses

Subgroup analyses were performed for age, disease duration, educational level and disease severity (according to two validated dementia ratings scales, or, when these were not available, with results of dementia screening tests) and are shown in supplementary tables e-5 – e-8. There was little influence of age, disease duration and education on any of the cognitive domains. Four analyses showed significant differences; more language deficits in younger patients, more attention deficits and less visuospatial deficits in patients with a lower educational level and more visuoconstruction deficits in patients with a shorter disease duration. As expected, the subgroup analysis for disease severity showed that patients with a more advanced disease had more cognitive deficits, although the only statistically significant difference was found in the verbal memory domain.

### Comparison of the cognitive profiles of bvFTD and ALS

First, we visually compared the effect sizes of the bvFTD and ALS meta-analyses, as shown in figure 2. As expected, the effect sizes of most cognitive domains and relevant neuropsychological tests were smaller in patients with ALS than in patients with bvFTD. In both disorders social cognition and fluency showed high effect sizes and visuoperception showed the lowest effect size. The confidence interval of the effect sizes of visuoconstruction in bvFTD overlapped with that of ALS, indicating that the patients with ALS were as impaired on these domains as the patients with bvFTD. The confidence intervals of psychomotor speed in bvFTD and ALS almost overlapped, indicating that both patient groups are similarly impaired in this domain. When the differences between the remaining effect sizes for each domain are considered (upper eight effect sizes in figure 2), the difference between the effect sizes of language between bvFTD and ALS is smaller, compared to that of other domains.

Second, Pearson's *r* correlation coefficient was calculated for all cognitive domains without bias due to motor impairment was 0.58 (p=0.13). We also calculated Pearson's *r* correlation coefficient for ALS-specific cognitive domains (social cognition, verbal memory, fluency, executive functions, language and

visuoperception), which was 0.73 (p=0.09). Pearson's *r* of the ALS-specific domains without language was 0.92 (p=0.03).

**Risk of bias**
The quality assessment with the Newcastle - Ottawa scale showed scores between 4 and 7 points (maximum score 9). In all but one study, patients and healthy volunteers were matched for age and education. The study without matching of patients and healthy volunteers used standardized scores. In all cognitive domains, the risk of a publication bias was low, i.e. the fail-safe N was at least two times higher than the tolerance level, which indicates that the presence of a publication bias is unlikely to have influenced the results.

## DISCUSSION

The current meta-analysis was performed to define the cognitive profile of bvFTD and to examine similarities with that of ALS. We chose to exclude language variants of FTLD to reduce heterogeneity and because they less often occur in combination with ALS.[6] The cognitive profile of bvFTD consists of deficits in social cognition, fluency and other executive functions and also includes verbal memory impairment, together with a relatively spared visuoperception. A comparison of the cognitive profiles of bvFTD and ALS shows similarities, notwithstanding cognitive deficits are more severe in patients with bvFTD in most domains. In both disorders, considerable impairment in social cognition, fluency and verbal memory was found, whereas impairment of visual memory and attention was less prominent with visuoperception showing the lowest level of impairment. The domains psychomotor speed and visuoconstructive functions behave in a different manner in bvFTD and ALS, which can be partly explained by physical impairment resulting in overestimation of psychomotor speed and visuoconstructive function deficits in patients with ALS.

**Social cognition in bvFTD**
The domain social cognition showed a large effect size in bvFTD and is thus an important component of the cognitive profile of bvFTD. Social cognition is a complex entity including theory of mind, which is the ability to infer mental states of others, such as their thoughts, beliefs and intentions.[28] Social cognition has a complex anatomical basis, including the frontostriatal network, temporo-occipital tracts, ventromedial prefrontal cortex and the amygdala, and therefore tests within this domain are highly mentally demanding.[29] The faux pas test, for example, consists of stories of approximately six to eight sentences and requires adequate attention and working memory (closely related to executive functioning).[30] In ALS, the presence of an association between deficits in





social cognition and executive dysfunction is unclear: a negative study (which specifically addressed this issue) is refuted by a recent meta-analysis of social cognition in ALS that showed an association between deficits in social cognition and executive functions.[5, 31]

In conclusion, social cognition involves high-level cognitive functioning and can be easily disrupted in bvFTD and ALS. One could argue that social cognition deficits are therefore likely to occur in early stages of bvFTD and ALS and may show progression over time.[32] This should be investigated in a longitudinal study including only early-stage bvFTD and patients with ALS. If confirmed, this could attribute to the early detection of cognitive impairment in patients with ALS.[29]

**Memory in bvFTD**
According to the consensus criteria for bvFTD, episodic memory is relatively spared in bvFTD.[10] Our findings of a large effect size for the domain verbal memory suggests that memory, in particular verbal memory, is less spared in bvFTD than previously thought. Previous findings of a similar degree of episodic memory deficits in patients with bvFTD and patients with Alzheimer's disease, and of severe memory deficits in amnestic variants of FTD, in combination with the findings of the current review, corroborate the thought that memory deficits are part of the cognitive profile of bvFTD.[33-36] Our data do not allow for a discussion of brain correlates of memory deficits in bvFTD and ALS – that is, whether memory deficits are predominantly associated with executive deficits related to frontal lobe dysfunction, or based on encoding difficulties related to hippocampal dysfunction. Nevertheless, the assumption that memory changes in bvFTD (and ALS) are primarily based on executive deficits is challenged by MRI studies in patients with early-stage bvFTD and ALS showing atrophy of the hippocampus, and pathological findings of inclusions in the dentate gyrus of the hippocampus in patients with ALS and bvFTD.[11, 37-40]

**Exploring heterogeneity**
There was considerable statistical heterogeneity in most cognitive domains. This can be partly explained by differences in study populations as a result of clinical variability – reflected, for example, by the results of the subgroup analysis 'disease severity.'

The clinical diagnosis bvFTD, according to consensus criteria, is based on the presence of abnormalities in three out of six domains of behavioural/cognitive symptoms. The presence of cognitive symptoms constitutes one of these six domains. Consequently, cognitive symptoms do not have be present in order to diagnose bvFTD, which has probably contributed to statistical heterogeneity

in our study.[10] This is further exemplified by wide confidence intervals of some cognitive domains of patients with bvFTD (e.g. social cognition, verbal memory and visual memory).

Besides clinical variability, other explanations for statistical heterogeneity in our study include the grouping of various neuropsychological tests into one domain. The classification of neuropsychological tests in different domains can be argued, as tests are never process-pure. We aimed for a functional classification, by using a-priori theory and convention to group the neuropsychological tests.[41] Furthermore, we grouped neuropsychological tests in agreement with other meta-analyses on cognitive impairment, and our own previous ALS meta-analysis, in order to enable a comparison between the bvFTD and ALS meta-analyses.[42-44]

Nevertheless, different sensitivities to pathology across tests can lead to diverging effect sizes of tests within a domain, and accordingly, a higher level of statistical heterogeneity. See for example different effect sizes in the social cognition domain of the Ekman test (Hedges' g = 1.89; CI 1.46 to 2.51) and theory of mind (Hedges' g = 0.85; CI 0.41 to 1.29).

**Comparison of the cognitive profiles of bvFTD and ALS**

Our study shows similarities between the cognitive profiles of bvFTD and ALS. The domains social cognition, verbal memory and fluency are most impaired in both diseases, with relative sparing of visuoperception. We also showed less severe language deficits in patients with bvFTD, compared to for example impairments in social cognition and verbal memory. In the ALS meta-analysis, we have shown that language impairment occurred frequently with one of the largest effect sizes. This difference between bvFTD and ALS can be explained by exclusion of language variants of FTD in the current meta-analysis. Although it is well known that a minority of patients with ALS develops semantic dementia or progressive non-fluent aphasia without behavioural changes, in this study we have chosen to include patients with the behavioural subtype of FTLD only.[45-47] We felt that inclusion of the language subtypes of FTLD would have led to a high level of heterogeneity (in particular regarding the language domain) and difficulties in interpreting the results. Furthermore the incidence of bvFTD in combination with ALS is higher than that of the language subtypes of FTLD.[48] The presence of a cognitive disease continuum between bvFTD and ALS could be corroborated when trajectories of cognitive deterioration are similar between the disorders. A relatively low number of longitudinal studies, however, prevented a meta-analysis of the courses of cognitive decline in ALS. A limited number of longitudinal neuropsychological studies in ALS so far, failed to show a consistent pattern of progression of cognitive deficits – longitudinal studies





on behavioural changes in ALS are even more scarce. These kinds of studies in patients with ALS are hampered by loss to follow-up due to progression of motor symptoms, including nocturnal hypoventilation or daytime hypercapnia due to respiratory insufficiency.[49-51] The latter complicates the interpretation of the nature of cognitive and behavioural changes in end-stage ALS. A future study in early-onset patients with ALS (i.e. disease duration < 1 year) with longitudinal (e.g. home-based) assessment of cognitive, behavioural and respiratory functions in late-stage ALS, may add relevant new information to the ongoing debate on the progression of cognitive deficits in ALS and the cognitive disease continuum between ALS and bvFTD.

**Limitations**

In addition to its strengths, i.e. a systematic analysis of a large number of studies, data extraction by two authors and a well-defined patient group, the current meta-analysis has some limitations, of which considerable heterogeneity in most cognitive domains has been described above.

The data does not allow for meta-analysing subgroups based on biomarker, genetic or pathological findings: in 8 (out of 120) included studies, the authors included and/or excluded (a proportion) of participants based on CSF findings (Aβ42, t and p-t, n=7)) or amyloid PET (n=3) results. Pathogenic mutations (MAPT, C9orf72 and PGRN) were reported in 5 articles. Therefore, it is not possible to draw conclusions about the cognitive profile of bvFTD and ALS subtypes based on these criteria.

Furthermore, some of the included studies were performed by the same research group. In order to prevent including the same patient group twice, we carefully checked the method sections of different papers by the same research group, in particular when longitudinal data were presented. Also, demographic characteristics and results of neuropsychological tests batteries performed by the same research group were compared, to exclude entirely similar cohorts. Although we cannot completely rule out the possibility that the same patient cohort was included twice, we are fairly confident that this is not the case. Also, because of the large number of participants and the robust results of the effect sizes and CIs, the inclusion of the same patient cohort would probably not significantly influence our results.

Finally, our findings do not exclude the possibility that the shared cognitive profile of ALS and bvFTD is a reflection of a common cognitive profile of neurodegenerative diseases in general, because we did not include other neurodegenerative disorders. To further investigate this we recommend comparisons of cognitive profiles of bvFTD and ALS with those of other

neurodegenerative diseases, such as Parkinson's disease and Huntington's disease.

In conclusion, we have determined the cognitive profile of bvFTD and have indicated that the cognitive profiles of bvFTD and ALS show similarities. The findings support the existence of a cognitive continuum between bvFTD and ALS and may direct cognitive testing of ALS and patients with bvFTD. Based on our meta-analytic results of individual tests, a combination of neuropsychological tests could be proposed to be used in patient care and scientific studies of bvFTD and patients with ALS. The following tests show relatively large effects sizes and low measures of heterogeneity within domains and, together, cover most of the cognitive changes in bvFTD and ALS: Ekman test (social cognition), auditory verbal learning test (verbal memory), letter fluency (fluency), Hayling test (executive functions), doors test (visual memory) and Boston naming test (language).

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# SUPPLEMENTAL MATERIAL

**Table e-1.** Key words used in the literature search

| | | |
|---|---|---|
| FTD, frontotemporal dementia, FTLD, pick's disease, frontal variant FTD, frontal variant dementia, bvFTD, f-FTD, frontotemporal (lobar) degeneration, presenile dementia | **OR** | amyotrophic lateral sclerosis, ALS, motor neuron(e) disease, MND, Gehrig |
| | **AND** | |
| cognition, mild cognitive impairment, cognition disorders, language disorders, (neuro) psychological tests, language (tests), memory, MMSE, Mini Mental State Examination, theory of mind, Frontal Assessment Battery, Boston Naming, Wisconsin Card Sorting Test, Stroop test, trail making test, aptitude tests | | |

**Table e-2.** Overview of tests used in the cognitive domains

| Cognitive domain | Cognitive skills tested within the cognitive domain | Frequently used neuropsychological tests within the cognitive domain |
|---|---|---|
| Social cognition | Social perception, recognition of expressed emotions, understanding social causality and theory of mind | Ekman 60 faces test, faux pas test, reading the mind in the eyes test, theory of mind, The Awareness of Social Inference Test |
| Verbal memory | Recall of unassociated words and short stories | Auditory verbal learning test, logical memory test, recognition memory test – words, free and cued selective reminding test |
| Fluency | Mental lexicon and executive control | Letter fluency, category fluency, design fluency |
| Executive functions | Mental flexibility, task-switching, strategic planning and suppression ability | Trail making test part B, stroop test part B, Iowa gambling test, Wisconsin card sorting test, hayling sentence completion test, brixton test |
| Visual memory | Visuospatial memory and visual recognition of objects and faces | Rey complex figure test part B, face recognition task, doors test, recognition memory test – faces |
| Visuoconstruction | Ability to copy complex figures | Rey complex figure test part A |
| Language | Naming and picture and word comprehension | Boston naming test, peabody picture vocabulary test, piramids and palm trees test, token test, western aphasia battery, Sydney language battery, British picture vocabulary scale |
| Attention | Verbal and visual working memory and associability | Digit span forward, digit span backward, visual span, letter number sequencing test |
| Psychomotor speed | Processing speed and mental flexibility | Trail making test part A, stroop test part A, symbol digit substitution test |
| Visuoperception | Object and space perception | Judgement of line orientation test, visual object and space perception battery |

Legend. Only frequently used tests are included in this table, i.e. tests used in three or more studies

**Table e-3.** Characteristics of the included articles

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Irish 2013[1] | 4 | 2 | 1 | 10/10 | 62.8 | 4.8 | 11.8 | 81.1# |
| Cruz de Souza 2010[2] | 3 | 2 | 1 | 17/17 | 71.1 | - | 5.2 | - |
| Chiong 2013[3] | 2 | 2 | 1 | 10/16 | 61.2 | - | 16.6 | 1.1*<br>6.1§ |
| Kumfor 2013[4] | 3 | 2 | 1 | 11/15 | 66.7 | 6.1 | 11.2 | 77.7# |
| Diehl-Schmid 2007[5] | 3 | 2 | 1 | 25/33 | 63.2 | - | 12.8 | - |
| Fine 2009[6] | 2 | 2 | 1 | 25/9 | 58.6 | - | 16.5 | - |
| O'Callaghan 2013[7] | 3 | 2 | 1 | 11/15 | 63.1 | 1.0 | 12.2 | - |
| Carey 2008[8] | 2 | 2 | 1 | 44/ 27 | 61.5 | - | 15.3 | - |
| Banks 2008[9] | 2 | 2 | 1 | 11/15 | 63.8 | 5.6 | 15.9 | - |
| Irish 2013[10] | 1 | 2 | 1 | 15/15 | 63.9 | 3.0 | 12.3 | 78.5# |
| Ash 2009[11] | 2 | 2 | 1 | 12/10 | 64.8 | 4.1 | 16.0 | - |
| Couto 2013[12] | 3 | 2 | 1 | 12/18 | 69.8 | - | 16.0 | - |
| Cosentino 2006[13] | 2 | 2 | 1 | 12/15 | 67.4 | 6.0 | 15.8 | - |
| Bertoux 2013[14] | 3 | 2 | 1 | 20/30 | 69.2 | 3.3 | 9.9 | - |
| Bertoux 2012[15] | 2 | 2 | 1 | 37/30 | 65.0 | - | 10.6 | 126.5$ |
| Collette 2007[16] | 2 | 2 | 1 | 13/28 | 65.7 | - | - | 127.3$ |
| Collette 2010[17] | 4 | 2 | 1 | 12/20 | 67.5 | - | 11.6 | 118.7$ |
| Fernandez-Duque 2005[18] | 2 | 2 | 1 | 6/10 | 63.7 | - | 16.5 | 125.7$ |
| Fernandez-Duque 2007[19] | 2 | 2 | 1 | 10/14 | 61,0 | - | 16.3 | - |

**Table e-3.** Continued.

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Fernandez-Duque 2009[20] | 2 | 2 | 1 | 11/12 | 60.6 | 3.4 | 16.1 | 126.4$ |
| Fernandez-Duque 2010[21] | 2 | 2 | 1 | 9/10 | 62.3 | - | 16.2 | 126.0$ |
| Filippi 2013[22] | 4 | 2 | 1 | 12/30 | 59.0 | 2.7 | 11.0 | 4.8§ |
| Downey 2013[23] | 3 | 2 | 1 | 20/20 | 64,0 | 5.5 | 13.0 | - |
| Funkiewiez 2012[24] | 3 | 2 | 1 | 22/30 | 65.5 | - | 5.3 | 131.4$ |
| Gleichgerrcht 2011[25] | 2 | 2 | 1 | 25/26 | 70.0 | - | 15.9 | 0.8*<br>80.1# |
| Gleichgerrcht 2012[26] | 4 | 2 | 1 | 35/14 | 68.5 | - | 13.6 | 81.9# |
| Gregory 2002[27] | 4 | 2 | 1 | 19/16 | 58.6 | - | 11.6 | 81.4# |
| Hodges 1999[28] | 3 | 2 | 1 | 9/9 | 57.0 | - | 10.0 | - |
| Hornberger 2011[29] | 3 | 2 | 1 | 14/18 | 59.3 | 3.7 | 11.8 | 75.6# |
| Hsieh 2012[30] | 3 | 2 | 1 | 8/15 | 62.9 | - | 12.3 | 1.4*<br>79.6# |
| Irish 2011[31] | 3 | 2 | 1 | 15/19 | 61.6 | 3.2 | 12.3 | 78.1# |
| Isella 2008[32] | 3 | 2 | 1 | 18/40 | 65.1 | - | 7.5 | 1.1* |
| Johns 2009[33] | 4 | 2 | 1 | 17/20 | 66.6 | - | 11.5 | - |
| Johnson 2011[34] | 3 | 2 | 1 | 11/17 | 59.8 | - | 16.2 | 6.1§ |
| Kloeters 2013[35] | 3 | 2 | 1 | 18/28 | 60.8 | - | 11.6 | 80.1# |
| Kugo 2007[36] | 3 | 2 | 1 | 23/25 | 64.7 | 5.0 | 11.2 | 1.3* |
| Kumfor 2011[37] | 3 | 2 | 1 | 16/37 | 61.5 | 3.5 | 12.1 | 82.8# |

**Table e-3.** Continued.

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Laisney 2009[38] | 2 | 2 | 1 | 18/18 | 67.2 | 2.7 | 11.2 | - |
| Le Bouc 2012[39] | 2 | 2 | 1 | 11/20 | 58.7 | - | 11.5 | - |
| Lough 2006[40] | 2 | 2 | 1 | 31/13 | 61.1 | - | - | 86.5# |
| Manes 2011[41] | 2 | 2 | 1 | 43/14 | 68.8 | - | 13.6 | 0.7*<br>78.9# |
| Matuszewski 2006[42] | 2 | 2 | 1 | 20/21 | 67.9 | - | - | - |
| McKinnon 2008[43] | 2 | 2 | 1 | 8/16 | 59.0 | 3.0 | 15.5 | - |
| Mendez 1998[44] | 3 | 2 | 1 | 31/31 | 65.6 | 2.7 | 14.1 | 1.4* |
| Miller 2012[45] | 3 | 2 | 1 | 17/36 | 61.0 | 3.7 | 12.0 | 86.0#<br>0.7* |
| Omar 2011[46] | 2 | 2 | 1 | 16/21 | 64.7 | 6.9 | 14.1 | - |
| Omar 2013[47] | 3 | 2 | 1 | 12/17 | 66.1 | - | - | - |
| Pachana 1996[48] | 2 | 2 | 1 | 15/16 | 63.9 | - | 15.2 | - |
| Peelle 2007[49] | 2 | 2 | 1 | 7/20 | 60.0 | - | 14.6 | - |
| Pennington 2011[50] | 2 | 2 | 1 | 14/15 | 59.7 | 3.4 | 10.5 | - |
| Possin 2012[51] | 3 | 2 | 1 | 32/37 | 59.4 | - | 16.6 | - |
| Possin 2011[52] | 4 | 2 | 1 | 48/94 | 61.8 | - | 16.6 | - |
| Rahman 1999[53] | 3 | 2 | 1 | 8/8 | 57.9 | 3.4 | - | - |
| Rankin 2009[54] | 3 | 2 | 1 | 20/13 | 60.0 | - | 16.7 | 1.1*<br>6.6§ |

**Table e-3.** Continued.

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Ricci 2012[55] | 3 | 2 | 1 | 15/28 | 65.7 | - | 10.3 | - |
| Ricci 2012[55] | 3 | 2 | 1 | 11/15 | 59.8 | - | 12.6 | - |
| Savage 2014[56] | 2 | 2 | 1 | 25/30 | 62.5 | - | 11.8 | 77.5# |
| Silveri 2003[57] | 2 | 2 | 1 | 17/34 | 72.1 | - | 8.9 | - |
| Souchay 2003[58] | 3 | 2 | 1 | 6/16 | 57.7 | - | 9.8 | - |
| Stopford 2012[59] | 4 | 2 | 1 | 26/26 | 64.0 | 6.0 | - | 1.0* |
| Torralva 2007[60] | 3 | 2 | 1 | 20/10 | 67.2 | - | 12.8 | 85.6# |
| Torralva 2009[61] | 3 | 2 | 1 | 35/14 | 67.2 | - | 13.6 | 81.9# |
| Viskontas 2011[62] | 2 | 2 | 1 | 12/21 | 61.2 | - | 15.3 | 0.9*<br>5.5§ |
| Wicklund 2004[63] | 3 | 2 | 1 | 16/20 | 65.1 | 4.4 | 15.7 | - |
| Baez 2014[64] | 2 | 2 | 1 | 37/30 | 66.0 | - | 13.7 | - |
| Bertoux 2014[65] | 3 | 2 | 1 | 44/22 | 67.0 | - | 11.0 | - |
| Hsieh 2013[66] | 3 | 2 | 1 | 9/15 | 62.5 | - | 10.9 | 4.9§ |
| Irish 2014[67] | 2 | 2 | 1 | 19/19 | 63.6 | 3.9 | 12.6 | 77.5# |
| Irish 2014[68] | 3 | 2 | 1 | 10/14 | 63.6 | 5.0 | 10.9 | 77.2# |
| Kamminga 2014[69] | 2 | 2 | 1 | 8/11 | 64.1 | 5.1 | 11.6 | 83.5# |
| Kumfor 2014[70] | 2 | 2 | 1 | 20/24 | 66.6 | 5.2 | 12.2 | 79.7# |
| Lagarde 2013[71] | 2 | 2 | 1 | 16/18 | 69.3 | 5.3 | 11.8 | 124.7§ |
| Lemos 2014[72] | 4 | 2 | 1 | 32/32 | 68.6 | - | 7.0 | 1.0* |

**Table e-3.** Continued.

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Russo 2014[73] | 3 | 2 | 1 | 27/40 | 66.5 | 3.3 | 13.6 | 6.2§ |
| Ash 2016[74] | 3 | 2 | 1 | 54/27 | 63.7 | 4.2 | 15.7 | - |
| Baez 2016[75] | 2 | 2 | 1 | 26/23 | 66.1 | - | 15.2 | - |
| Baez 2017[76] | 2 | 2 | 1 | 16/22 | 65.8 | - | 14.8 | - |
| Balconi 2015[77] | 2 | 2 | 1 | 16/20 | 65.6 | - | 7.0 | - |
| Bertoux 2016[78] | 2 | 2 | 1 | 71/60 | 65.9 | 3.3 | 11.4 | - |
| Bertoux 2015[79] | 2 | 2 | 1 | 60/30 | 66.1 | 3.2 | 10.3 | - |
| Brioschi 2015[80] | 2 | 2 | 1 | 28/18 | 59.2 | - | 15.9 | - |
| Cavedo 2014[81] | 3 | 2 | 1 | 16/22 | 69.0 | - | 12.0 | - |
| Cerciello 2017[82] | 2 | 2 | 1 | 9/20 | 72.3 | - | 9.5 | - |
| Chiong 2016[83] | 2 | 2 | 1 | 25/58 | 64.0 | - | 16.9 | 7.0§ |
| Clark 2015[84] | 3 | 2 | 1 | 22/21 | 67.0 | 9 | 13.9 | - |
| Clark 2015[85] | 2 | 2 | 1 | 15/21 | 65.0 | 6.3 | 17.0 | - |
| Cohen 2016[86] | 2 | 2 | 1 | 11/39 | 68.0 | 8.5 | 10.2 | - |
| Consonni 2017[87] | 2 | 2 | 1 | 15/48 | 64.4 | 3.5 | - | - |
| Cook 2014[88] | 2 | 2 | 1 | 33/15 | 62.0 | 5 | 16.0 | - |
| Custodio 2016[89] | 3 | 2 | 1 | 34/25 | 67.1 | - | 11.7 | 0.8*<br>76.6# |
| Dermody 2016[90] | 3 | 2 | 1 | 24/22 | 63.0 | 3.5 | 12.4 | 74.2# |
| Dermody 2015[91] | 4 | 2 | 1 | 12/12 | 63.2 | 5.1 | 11.6 | 78.8# |

**Table e-3.** Continued.

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Fernandez 2017[92] | 3 | 2 | 1 | 26/24 | 71.3 | 3.9 | 8.0 | 70.4# |
| Flanagan 2016[93] | 3 | 2 | 1 | 39/61 | 60.6 | 3.5 | 12.3 | - |
| Fletcher 2015[94] | 2 | 2 | 1 | 16/26 | 66.0 | 8.3 | 14.6 | - |
| Hafkemeijer 2017[95] | 2 | 2 | 1 | 12/22 | 64.7 | 5.0 | - | 1.3* |
| Hardy 2016[96] | 2 | 2 | 1 | 24/24 | 64.4 | 7.8 | 14.8 | - |
| Hutchings 2015[97] | 2 | 2 | 1 | 16/17 | 64.1 | 5.1 | 11.8 | - |
| Irish 2016[98] | 3 | 2 | 1 | 15/20 | 63.5 | 3.8 | 11.6 | 79.4# |
| Johnen 2016[99] | 4 | 2 | 1 | 24/35 | 64.9 | 2.7 | 11.2 | - |
| Kamminga 2015[100] | 3 | 2 | 1 | 19/20 | 60.5 | 4.3 | 11.3 | 79.0# |
| Keri 2014[101] | 4 | 2 | 1 | 16/20 | 58.9 | - | 11.7 | - |
| Kumfor 2015[102] | 4 | 2 | 1 | 13/11 | 62.5 | 5.5 | 12.0 | 77.0# |
| Kumfor 2016[103] | 3 | 2 | 1 | 13/16 | 60.2 | 4.3 | 11.8 | 77.5# |
| Lagarde 2015[104] | 3 | 2 | 1 | 18/18 | 69.7 | 5.4 | 12.0 | 126.3$ |
| Leslie 2016[105] | 4 | 2 | 1 | 14/33 | 62.7 | 4.8 | 12.2 | 68.2# |
| Lin 2016[106] | 2 | 2 | 1 | 15/15 | 62.1 | 5.1 | 11.4 | - |
| Mahoney 2015[107] | 3 | 2 | 1 | 23/18 | 63.8 | - | 15.5 | - |
| Mandelli 2016[108] | 3 | 2 | 1 | 23/34 | 62.9 | - | 16.1 | - |
| Metzger 2016[109] | 3 | 2 | 1 | 8/8 | 67.6 | - | - | - |
| O'Callaghan 2016[110] | 3 | 2 | 1 | 22/22 | 64.8 | 2.3 | 12.0 | - |
| Primativo 2017[111] | 2 | 2 | 1 | 12/38 | 67.7 | 9.2 | 14.0 | - |

**Table e-3.** Continued.

| Author, year | Newcastle Ottawa scale | | | Participants (p/c) | Age of patients | Disease duration | Years of education | Disease severity |
|---|---|---|---|---|---|---|---|---|
| | Selection | Comparability | Exposure | | | | | |
| Ramanan 2015[112] | 4 | 2 | 1 | 17/35 | 67.0 | 3.0 | 15.8 | 1.37*<br>62.3# |
| Santamaria-Garcia 2017[113] | 2 | 2 | 1 | 20/20 | 58.9 | 3.1 | 14.8 | - |
| Scherling 2017[114] | 3 | 2 | 1 | 17/35 | 62.1 | - | 16.5 | 6.4§ |
| Sedeno 2016[115] | 2 | 2 | 1 | 14/12 | 66.4 | - | 14.7 | - |
| Tan 2015[116] | 3 | 2 | 1 | 23/15 | 62.0 | 4.0 | 12.0 | 74.0# |
| Torralva 2015[117] | 4 | 2 | 1 | 40/18 | 67.2 | - | 15.0 | 70.4# |
| Tu 2015[118] | 3 | 2 | 1 | 24/23 | 64.7 | 6.6 | 11.8 | 82.1# |
| Wong 2014[119] | 3 | 2 | 1 | 22/35 | 61.2 | 3.8 | 11.3 | 7.1§<br>76.0# |
| Wong 2016[120] | 3 | 2 | 1 | 22/38 | 61.0 | 3.6 | 11.8 | 5.6§<br>76.3# |

Legend. NOS: Newcastle Ottawa scale (maximum score 8); p: patients; c: controls. Age and disease durations are expressed in years. Disease severity is expressed as scores on the Clinical Dementia Rating scale (CDR*; scores from 0 to 3, higher scores indicate more impairment, mean score was 1.1, indicating mild dementia[121]), Addenbrooke's Cognitive Examination – Revised (ACE-R#; scores from 0 to 100, higher scores indicate better performance, mean score was 78.1, indicating moderate dementia[122]), CDR sum of boxes§ (scores from 0 to 18, higher scores indicate more impairment, mean score was 6.0, indicating mild dementia[123]) and the Mattis Dementia Rating Scale (MDRS$; scores from 0 to 144, higher score indicate better performance, mean score was 125.9, indicating no dementia[124]).





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**Table e-4.** Articles excluded from the meta-analysis

| | | | |
|---|---|---|---|
| Blair | 2007 | Dementia & Geriatric Cognitive Disorders | ALS-FTD patients included in patient group |
| Cantoni | 2010 | Journal of Alzheimer's Disease | ALS-FTD patients included in patient group |
| Cardenas | 2007 | Archives of Neurology | ALS-FTD patients included in patient group |
| Chow | 2008 | Alzheimer Disease & Associated Disorders | ALS-FTD patients included in patient group |
| Hartikainen | 2012 | Journal of Alzheimer's Disease | ALS-FTD patients included in patient group |
| Ishii | 1998 | Journal of Nuclear Medicine | ALS-FTD patients included in patient group |
| Munoz-Ruiz | 2013 | Journal of Alzheimer's Disease | ALS-FTD patients included in patient group |
| Munoz-Ruiz | 2012 | PLoS ONE | ALS-FTD patients included in patient group |
| Seeley | 2008 | Archives of Neurology | ALS-FTD patients included in patient group |
| Zhang | 2009 | Brain | ALS-FTD patients included in patient group |
| Zhou | 2010 | Brain | ALS-FTD patients included in patient group |
| Bruno | 2017 | Neurologia | Article in Spanish |
| Cossini | 2016 | Neurologia Argentina | Article in Spanish |
| Martinez | 2015 | Revista Colombiana De Psiquiatria | Article in Spanish |
| Pollitis | 2016 | Vertex | Article in Spanish |
| Turro-Garriga | 2017 | Neurologia | Article in Spanish |
| Agosta | 2015 | Human Brain Mapping | Control group not matched for age or education |
| Agosta | 2013 | Neurology | Control group not matched for age or education |
| Agosta | 2009 | Proceedings of the National Academy of Sciences | Control group not matched for age or education |
| Ahmed | 2016 | Journal of Neurology, Neurosurgery and Psychiatry | Control group not matched for age or education |
| Allali | 2010 | Movement Disorders | Control group not matched for age or education |
| Anderson | 2009 | European Journal of Neurology | Control group not matched for age or education |
| Bak | 2003 | Journal of Neurolinguistics | Control group not matched for age or education |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Baldeiras | 2015 | Journal of the Neurological Sciences | Control group not matched for age or education |
| Basely | 2013 | European Journal of Nuclear Medicine & Molecular Imaging | Control group not matched for age or education |
| Bastin | 2012 | Human Brain Mapping | Control group not matched for age or education |
| Bernardi | 2006 | Neurobiology of Aging | Control group not matched for age or education |
| Bertoux | 2012 | Journal of the International Neuropsychological Society | Control group not matched for age or education |
| Bertoux | 2015 | Neuropsychology | Control group not matched for age or education |
| Bird | 2010 | Hippocampus | Control group not matched for age or education |
| Boccardi | 2005 | Neurobiology of Aging | Control group not matched for age or education |
| Buerger | 2002 | Archives of Neurology | Control group not matched for age or education |
| Cappa | 1998 | Neurology | Control group not matched for age or education |
| Chan | 2015 | Psychiatry Research | Control group not matched for age or education |
| Chiu | 2012 | Journal of Neurology | Control group not matched for age or education |
| De Souza | 2013 | Journal of Alzheimer's Disease | Control group not matched for age or education |
| De winter | 2016 | NeuroImage: clinical | Control group not matched for age or education |
| Derouesne | 2012 | Geriatrie Et Psychologie Neuropsychiatrie Du Vieillissement | Control group not matched for age or education |
| Donaghy | 2010 | Journal of Neurology | Control group not matched for age or education |
| Downey | 2015 | NeuroImage: clinical | Control group not matched for age or education |
| Du | 2007 | Brain | Control group not matched for age or education |
| Du | 2006 | Neurology | Control group not matched for age or education |
| Eckart | 2012 | Neuropsychologia | Control group not matched for age or education |
| Eslinger | 2007 | Journal of Neurology | Control group not matched for age or education |
| Filippi | 2017 | Neurology | Control group not matched for age or education |
| Foley | 2008 | Acta Neuropsychiatrica | Control group not matched for age or education |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Freedman | 2013 | Alzheimer Disease & Associated Disorders | Control group not matched for age or education |
| Freedman | 2013 | Alzheimer Disease & Associated Disorders | Control group not matched for age or education |
| Frings | 2012 | Human Brain Mapping | Control group not matched for age or education |
| Frisoni | 1996 | Journal of Neurology | Control group not matched for age or education |
| Gennatas | 2012 | Neurology | Control group not matched for age or education |
| Giovagnoli | 2008 | Neuropsychologia | Control group not matched for age or education |
| Gola | 2017 | NeuroImage: clinical | Control group not matched for age or education |
| Gordon | 2010 | Neurology | Control group not matched for age or education |
| Grossman | 2005 | Annals of Neurology | Control group not matched for age or education |
| Grossman | 2010 | Neuropsychologia | Control group not matched for age or education |
| Hansson | 2009 | Journal of Alzheimer's Disease | Control group not matched for age or education |
| Hazif-Thomas | 2005 | Annales medico-psychologiques | Control group not matched for age or education |
| Henley | 2014 | Neuropsychologia | Control group not matched for age or education |
| Hoefer | 2008 | Brain | Control group not matched for age or education |
| Hornberger | 2010 | Neurology | Control group not matched for age or education |
| Hughes | 2013 | Journal of Cognitive Neuroscience | Control group not matched for age or education |
| Irish | 2017 | Neuropsychologia | Control group not matched for age or education |
| Irish | 2014 | PLoS ONE | Control group not matched for age or education |
| Irish | 2014 | PLoS ONE | Control group not matched for age or education |
| Jastorff | 2016 | Human Brain Mapping | Control group not matched for age or education |
| Khan | 2012 | Journal of Neurology | Control group not matched for age or education |
| Kipps | 2009 | Brain | Control group not matched for age or education |
| Kipps | 2009 | Brain | Control group not matched for age or education |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Kramer | 2007 | Journal of the International Neuropsychological Society | Control group not matched for age or education |
| Krueger | 2010 | Alzheimer Disease & Associated Disorders | Control group not matched for age or education |
| Kumfor | 2017 | Cortex | Control group not matched for age or education |
| Kumfor | 2014 | Frontiers in Behavioral Neuroscience | Control group not matched for age or education |
| Kumfor | 2014 | Frontiers in Behavioral Neuroscience | Control group not matched for age or education |
| Lansdall | 2017 | Brain | Control group not matched for age or education |
| Lee | 2003 | European Journal of Neuroscience | Control group not matched for age or education |
| Lehmann | 2011 | Handbook of Imaging the Alzheimer Brain | Control group not matched for age or education |
| Looi | 2008 | American Journal of Neuroradiology | Control group not matched for age or education |
| Lorenzl | 2008 | International Psychogeriatrics | Control group not matched for age or education |
| Luks | 2010 | Neuropsychologia | Control group not matched for age or education |
| Macfarlane | 2015 | PLoS ONE | Control group not matched for age or education |
| Magerova | 2014 | American Journal of Alzheimer's Disease & Other Dementias | Control group not matched for age or education |
| Magerova | 2014 | American Journal of Alzheimer's Disease & Other Dementias | Control group not matched for age or education |
| Mahoney | 2014 | Human Brain Mapping | Control group not matched for age or education |
| Mahoney | 2014 | Human Brain Mapping | Control group not matched for age or education |
| Marshall | 2017 | Frontiers in Neurology | Control group not matched for age or education |
| Meijboom | 2017 | Europian Radiology | Control group not matched for age or education |
| Munoz-Ruiz | 2016 | Dementia & Geriatric Cognitive Disorders | Control group not matched for age or education |
| Murtha | 2002 | Journal of the International Neuropsychological Society | Control group not matched for age or education |
| Perneczky | 2013 | Translational Psychiatry | Control group not matched for age or education |
| Perry | 2015 | Alzheimer Disease & Associated Disorders | Control group not matched for age or education |
| Perry | 2012 | European Journal of Neurology | Control group not matched for age or education |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Perry | 2000 | Neurology | Control group not matched for age or education |
| Piguet | 2011 | Annals of Neurology | Control group not matched for age or education |
| Piquard | 2009 | Brain and Cognition | Control group not matched for age or education |
| Piquard | 2004 | Psychologie & Neuropsychiatrie du Vieillissement | Control group not matched for age or education |
| Porter | 2003 | Journal of Neuropsychiatry & Clinical Neurosciences | Control group not matched for age or education |
| Possin | 2013 | Neurology | Control group not matched for age or education |
| Ramanan | 2017 | Journal of the International Neuropsychological Society | Control group not matched for age or education |
| Ranjith | 2010 | Annals of Indian Academy of Neurology | Control group not matched for age or education |
| Rankin | 2007 | Cognitive & Behavioral Neurology | Control group not matched for age or education |
| Rankin | 2005 | Cognitive & Behavioral Neurology | Control group not matched for age or education |
| Richards | 2009 | Neurobiology of Aging | Control group not matched for age or education |
| Rosen | 2004 | Dementia and Geriatric Cognitive Disorders | Control group not matched for age or education |
| Rosen | 2002 | Neurology | Control group not matched for age or education |
| Rosen | 2014 | Neuropsychology | Control group not matched for age or education |
| Rosen | 2014 | Neuropsychology | Control group not matched for age or education |
| Rytty | 2013 | Frontiers in Human Neuroscience | Control group not matched for age or education |
| Santillo | 2013 | PLoS ONE | Control group not matched for age or education |
| Schubert | 2016 | Journal of Alzheimer's Disease | Control group not matched for age or education |
| Sebastian | 2010 | Psicothema | Control group not matched for age or education |
| Sebastian | 2012 | Psicothema | Control group not matched for age or education |
| Serrano | 2014 | Current Psychopharmacology | Control group not matched for age or education |
| Shany-Ur | 2014 | Brain | Control group not matched for age or education |
| Shany-Ur | 2012 | Cortex | Control group not matched for age or education |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Shimizu | 2010 | Brain Imaging & Behavior | Control group not matched for age or education |
| Silajdzic | 2012 | PLoS ONE | Control group not matched for age or education |
| Simonsen | 2007 | Dementia and Geriatric Cognitive Disorders | Control group not matched for age or education |
| Snowden | 2008 | Neuropsychologia | Control group not matched for age or education |
| Sollberger | 2014 | Brain and Behavior | Control group not matched for age or education |
| Sturm | 2017 | Brain and Behavior | Control group not matched for age or education |
| Thomas | 2009 | Encephale | Control group not matched for age or education |
| Thomas-Anterion | 1998 | Revue de Neuropsychologie | Control group not matched for age or education |
| Tosun | 2016 | Annals of Clinical and Translational Neurology | Control group not matched for age or education |
| Tu | 2017 | Journal of Alzheimer's Disease | Control group not matched for age or education |
| Valverde | 2009 | Clinical Neurology and Neurosurgery | Control group not matched for age or education |
| van den Stock | 2015 | Neuropsychologia | Control group not matched for age or education |
| Virani | 2013 | Journal of Psychiatry & Neuroscience | Control group not matched for age or education |
| Vogel | 2017 | Neurology | Control group not matched for age or education |
| Walker | 2005 | International Psychogeriatrics | Control group not matched for age or education |
| Walterfang | 2014 | Journal of Alzheimer's Disease | Control group not matched for age or education |
| Wang | 2016 | Frontiers in Aging Neuroscience | Control group not matched for age or education |
| Waragai | 2008 | Dementia & Geriatric Cognitive Disorders | Control group not matched for age or education |
| Weiner | 2011 | International Psychogeriatrics | Control group not matched for age or education |
| Whitwell | 2005 | Dementia & Geriatric Cognitive Disorders | Control group not matched for age or education |
| Wicklund | 2006 | Alzheimer Disease & Associated Disorders | Control group not matched for age or education |
| Wong | 2017 | Cortex | Control group not matched for age or education |
| Wong | 2017 | Neuropsychologia | Control group not matched for age or education |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Woolley | 2015 | Biological Psychiatry | Control group not matched for age or education |
| Woolley | 2012 | Current Alzheimer Research | Control group not matched for age or education |
| Yew | 2013 | Journal of Alzheimer's Disease | Control group not matched for age or education |
| Yoshida | 2009 | Dementia & Geriatric Cognitive Disorders | Control group not matched for age or education |
| Yoshida | 2011 | Psychiatry Research | Control group not matched for age or education |
| Koikkalainen | 2016 | NeuroImage: clinical | Controls with subjective cognitive complaints |
| Smits | 2015 | Psychological Medicine | Controls with subjective cognitive complaints |
| Teichmann | 2017 | Alzheimer's & Dementia | Controls with subjective cognitive complaints |
| Vijverberg | 2017 | Neurobiology of Aging | Controls with subjective cognitive complaints |
| Arslan | 2015 | Turkish Journal of Medical sciences | Did not meet validated clinical criteria |
| Hampel | 2004 | Archives of General Psychiatry | Did not meet validated clinical criteria |
| Serrano | 2014 | Current Psychopharmacology | Did not meet validated clinical criteria |
| Starkstein | 1994 | Journal of Neurology | Did not meet validated clinical criteria |
| Strenziok | 2011 | Cognitive & Behavioral Neurology | Did not meet validated clinical criteria |
| Bertoux | 2015 | Journal of Neurology, Neurosurgery and Psychiatry | Editorial |
| Bocchetta | 2016 | Journal of Neurology, Neurosurgery and Psychiatry | Editorial |
| Ahmed | 2016 | JAMA Neurology | Effect size calculation not possible |
| Alberici | 2014 | Neurological Sciences | Effect size calculation not possible |
| Andersen | 1997 | Archives of Neurology | Effect size calculation not possible |
| Appels | 2016 | Tijdschift voor Gerontologie en Geriatrie | Effect size calculation not possible |
| Avants | 2014 | NeuroImage | Effect size calculation not possible |
| Baez | 2014 | JAMA Neurology | Effect size calculation not possible |
| Barrows | 2015 | Journal of Geriatric Psychiatry & Neurology | Effect size calculation not possible |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Barsuglia | 2014 | Archives of Clinical Neuropsychology | Effect size calculation not possible |
| Beck | 2014 | International Journal of Geriatric Psychiatry | Effect size calculation not possible |
| Bediou | 2012 | Frontiers in Psychology | Effect size calculation not possible |
| Bertoux | 2014 | Biological Psychiatry | Effect size calculation not possible |
| Bertoux | 2013 | Brain Imaging & Behavior | Effect size calculation not possible |
| Bertoux | 2014 | Brain Imaging & Behavior | Effect size calculation not possible |
| Bertoux | 2015 | Journal of Alzheimer's Disease | Effect size calculation not possible |
| Binney | 2017 | Brain and Behavior | Effect size calculation not possible |
| Bladock | 2016 | Dementia and Geriatric Cognitive Disorders | Effect size calculation not possible |
| Borroni | 2015 | Neurobiology of Aging | Effect size calculation not possible |
| Brenowitz | 2014 | Journal of Alzheimer's Disease | Effect size calculation not possible |
| Caminiti | 2015 | NeuroImage: clinical | Effect size calculation not possible |
| Carnaghi | 2015 | Cognitive & Behavioral Neurology | Effect size calculation not possible |
| Carr | 2015 | Neuropsychologia | Effect size calculation not possible |
| Casaletto | 2017 | Neuropsychologia | Effect size calculation not possible |
| Cerami | 2014 | Alzheimer's & Dementia | Effect size calculation not possible |
| Cerami | 2015 | PLoS ONE | Effect size calculation not possible |
| Cismaru | 1999 | Brain and Cognition | Effect size calculation not possible |
| Croisile | 2010 | Revue Neurologique | Effect size calculation not possible |
| Devenny | 2015 | JAMA Neurology | Effect size calculation not possible |
| Dodich | 2016 | Journal of Alzheimer's Disease | Effect size calculation not possible |
| Dodich | 2014 | Neurological Sciences | Effect size calculation not possible |
| Eslinger | 2005 | Journal of Neurology | Effect size calculation not possible |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Eslinger | 2011 | Journal of Neuropsychiatry & Clinical Neurosciences | Effect size calculation not possible |
| Fletcher | 2016 | Cortex | Effect size calculation not possible |
| Freitas | 2015 | Archives of Clinical Neuropsychology | Effect size calculation not possible |
| Freitas | 2014 | Clinical Neuropsychologist | Effect size calculation not possible |
| Freitas | 2014 | Clinical Neuropsychologist | Effect size calculation not possible |
| Galimberti | 2012 | Neurodegenerative Disease Management | Effect size calculation not possible |
| Gola | 2015 | Neuropsychologia | Effect size calculation not possible |
| Hafkemeijer | 2015 | Frontiers in Human Neuroscience | Effect size calculation not possible |
| Hou | 2005 | International Journal of Geriatric Psychiatry | Effect size calculation not possible |
| Hsieh | 2013 | Dementia and Geriatric Cognitive Disorders | Effect size calculation not possible |
| Jahn | 2011 | PLoS ONE | Effect size calculation not possible |
| Jiskoot | 2016 | Neurology | Effect size calculation not possible |
| Josephs | 2009 | Neurology | Effect size calculation not possible |
| Kanda | 2008 | European Journal of Nuclear Medicine & Molecular Imaging | Effect size calculation not possible |
| Kimura | 1999 | Neuroscience Letters | Effect size calculation not possible |
| Kipps | 2009 | Neurocase | Effect size calculation not possible |
| Krawczyk | 2008 | Neuropsychologia | Effect size calculation not possible |
| Lagarde | 2013 | Journal of Neurology | Effect size calculation not possible |
| Lima-Silva | 2015 | Journal of Geriatric Psychiatry & Neurology | Effect size calculation not possible |
| Lindberg | 2009 | American Journal of Neuroradiology | Effect size calculation not possible |
| Looi | 2009 | American Journal of Neuroradiology | Effect size calculation not possible |
| Looi | 2010 | NeuroImage | Effect size calculation not possible |
| Looi | 2011 | Psychiatry Research | Effect size calculation not possible |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| McCawley | 2005 | Brain and Language | Effect size calculation not possible |
| McMillan | 2004 | Dementia and Geriatric Cognitive Disorders | Effect size calculation not possible |
| Meijboom | 2017 | Journal of Alzheimer's Disease | Effect size calculation not possible |
| Moller | 2016 | Neurobiology of Aging | Effect size calculation not possible |
| Moller | 2015 | NeuroImage: clinical | Effect size calculation not possible |
| Moller | 2016 | Radiology | Effect size calculation not possible |
| Munoz-Neira | 2014 | International Journal of Geriatric Psychiatry | Effect size calculation not possible |
| Novellino | 2010 | Neurobiology of Aging | Effect size calculation not possible |
| Peelle | 2008 | Journal of Neurolinguistics | Effect size calculation not possible |
| Piolino | 2003 | Brain | Effect size calculation not possible |
| Ranasinghe | 2016 | Neurology | Effect size calculation not possible |
| Rankin | 2011 | Journal of Molecular Neuroscience | Effect size calculation not possible |
| Reul | 2017 | Alzheimer's Research & Therapy | Effect size calculation not possible |
| Reverberi | 2014 | Cortex | Effect size calculation not possible |
| Rodell | 2016 | Frontiers in Aging Neuroscience | Effect size calculation not possible |
| Rogers | 2006 | Neuropsychology | Effect size calculation not possible |
| Rohrer | 2016 | Neurology | Effect size calculation not possible |
| Rousseaux | 2010 | Neuropsychologia | Effect size calculation not possible |
| Rowe | 2007 | Neurology | Effect size calculation not possible |
| Schmidtke | 2007 | International Psychogeriatrics | Effect size calculation not possible |
| Seelaar | 2011 | Neurology | Effect size calculation not possible |
| Serpente | 2015 | International Journal of Molecular Science | Effect size calculation not possible |
| Sharma | 2011 | Indian Journal of Nuclear Medicine | Effect size calculation not possible |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Silveri | 2003 | Dementia and Geriatric Cognitive Disorders | Effect size calculation not possible |
| Sjogren | 2000 | Neurology | Effect size calculation not possible |
| Steketee | 2016 | NeuroImage: clinical | Effect size calculation not possible |
| Stopford | 2010 | Behavioural Neurology | Effect size calculation not possible |
| Tan | 2013 | Dementia & Geriatric Cognitive Disorders | Effect size calculation not possible |
| Vijverberg | 2017 | Journal of Clinical Psychiatry | Effect size calculation not possible |
| Watanabe | 2016 | Journal of the Neurological Sciences | Effect size calculation not possible |
| Whitwell | 2011 | Journal of Molecular Neuroscience | Effect size calculation not possible |
| Whitwell | 2009 | Neurodegenerative Disease | Effect size calculation not possible |
| Wong | 2014 | PLoS ONE | Effect size calculation not possible |
| Alberici | 2007 | Neurological Sciences | FTLD patients included in patient group |
| Alexopoulos | 2010 | Dementia & Geriatric Cognitive Disorders | FTLD patients included in patient group |
| Anauate | 2014 | Dementia & Neuropsychologia | FTLD patients included in patient group |
| Anauate | 2014 | Dementia & Neuropsychologica | FTLD patients included in patient group |
| Ash | 2005 | Brain and Language | FTLD patients included in patient group |
| Avants | 2010 | NeuroImage | FTLD patients included in patient group |
| Barnes | 2006 | Archives of Neurology | FTLD patients included in patient group |
| Beber | 2013 | Dementia & Neuropsychologia | FTLD patients included in patient group |
| Bediou | 2009 | Journal of Geriatric Psychiatry & Neurology | FTLD patients included in patient group |
| Bellassen | 2012 | Journal of Neuroscience | FTLD patients included in patient group |
| Benussi | 2017 | Neurology | FTLD patients included in patient group |
| Binetti | 2000 | Archives of Neurology | FTLD patients included in patient group |
| Blair | 2006 | Journal of the International Neuropsychological Society | FTLD patients included in patient group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Boban | 2012 | Journal of Geriatric Psychiatry & Neurology | FTLD patients included in patient group |
| Bocti | 2006 | Dementia & Geriatric Cognitive Disorders | FTLD patients included in patient group |
| Bourbouli | 2017 | Dementia and Geriatric Cognitive Disorders | FTLD patients included in patient group |
| Boxer | 2012 | Archives of Neurology | FTLD patients included in patient group |
| Bozzali | 2013 | Journal of Alzheimer's Disease | FTLD patients included in patient group |
| Burrell | 2012 | Neurology | FTLD patients included in patient group |
| Busse | 2014 | Neuroscience Research | FTLD patients included in patient group |
| Carlino | 2014 | NeuroReport | FTLD patients included in patient group |
| Chan | 2009 | Brain | FTLD patients included in patient group |
| Chow | 2008 | Dementia and Geriatric Cognitive Disorders | FTLD patients included in patient group |
| Comi | 2010 | Journal of Alzheimer's Disease | FTLD patients included in patient group |
| Cooke | 2003 | Brain and Language | FTLD patients included in patient group |
| Craig-Schapiro | 2010 | Biological Psychiatry | FTLD patients included in patient group |
| Dalton | 2013 | NeuroImage: clinical | FTLD patients included in patient group |
| Darvesh | 2005 | Canadian Journal of Neurological Sciences | FTLD patients included in patient group |
| Davatzikos | 2008 | NeuroImage | FTLD patients included in patient group |
| Davis | 2010 | Neurocase | FTLD patients included in patient group |
| de Boysson | 2011 | Brain and Cognition | FTLD patients included in patient group |
| de Simone | 2007 | Dementia and Geriatric Cognitive Disorders | FTLD patients included in patient group |
| Desphande | 2004 | Brain and Cognition | FTLD patients included in patient group |
| Diehl | 2005 | Aktuelle Neurologie | FTLD patients included in patient group |
| Dubois | 2000 | Neurology | FTLD patients included in patient group |
| Dudas | 2005 | American Journal of Geriatric Psychiatry | FTLD patients included in patient group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Dukarts | 2010 | NeuroImage | FTLD patients included in patient group |
| Economou | 2016 | Alzheimer Disease & Associated Disorders | FTLD patients included in patient group |
| Frings | 2011 | Current Alzheimer Research | FTLD patients included in patient group |
| Frisch | 2013 | PLoS ONE | FTLD patients included in patient group |
| Galimberti | 2008 | Journal of Neurology | FTLD patients included in patient group |
| Ghidoni | 2008 | Neurology | FTLD patients included in patient group |
| Goodkind | 2010 | Psychology & Aging | FTLD patients included in patient group |
| Grieder | 2013 | Journal of Alzheimer's Disease | FTLD patients included in patient group |
| Grossman | 1996 | Neurology | FTLD patients included in patient group |
| Gyurak | 2012 | Cognition and Emotion | FTLD patients included in patient group |
| Gyurak | 2009 | Cognitive, Affective, & Behavioral Neuroscience | FTLD patients included in patient group |
| Hailstone | 2010 | Behavioural Neurology | FTLD patients included in patient group |
| Halpern | 2007 | Brain and Cognition | FTLD patients included in patient group |
| Halpern | 2003 | Journal of the Neurological Sciences | FTLD patients included in patient group |
| Hoffmann | 2013 | American Journal of Alzheimer's Disease & Other Dementias | FTLD patients included in patient group |
| Honda | 2013 | International Psychogeriatrics | FTLD patients included in patient group |
| Huey | 2015 | Cortex | FTLD patients included in patient group |
| Jagust | 1989 | American Journal of Physiologic Imaging | FTLD patients included in patient group |
| Jimenez-Escrig | 2002 | Dementia and Geriatric Cognitive Disorders | FTLD patients included in patient group |
| Johanson | 1990 | Dementia | FTLD patients included in patient group |
| Kantarci | 2004 | Neurology | FTLD patients included in patient group |
| Karjalainen | 2005 | Logopedics | FTLD patients included in patient group |
| Kessels | 2007 | Behavioural Neurology | FTLD patients included in patient group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Kim | 2007 | Journal of Neurology | FTLD patients included in patient group |
| Kortvelyessy | 2015 | Journal of Alzheimer's Disease | FTLD patients included in patient group |
| Lehmann | 2010 | Journal of Alzheimer's Disease | FTLD patients included in patient group |
| Lipton | 2001 | Archives of Neurology | FTLD patients included in patient group |
| Mathuranath | 2000 | Neurology | FTLD patients included in patient group |
| McLaughlin | 2008 | Archives of Clinical Neuropsychology | FTLD patients included in patient group |
| Mioshi | 2013 | Journal of Geriatric Psychiatry & Neurology | FTLD patients included in patient group |
| Moon | 2008 | American Journal of Neuroradiology | FTLD patients included in patient group |
| Murray | 2005 | Brain and Language | FTLD patients included in patient group |
| Narme | 2013 | Journal of Clinical & Experimental Neuropsychology | FTLD patients included in patient group |
| O'Keeffe | 2007 | Brain | FTLD patients included in patient group |
| Oliver | 2014 | Neuropsychologia | FTLD patients included in patient group |
| Oliver | 2014 | Neuropsychologia | FTLD patients included in patient group |
| Oliver | 2015 | Neuropsychologia | FTLD patients included in patient group |
| Pakhomov | 2011 | Journal of Neurolinguistics | FTLD patients included in patient group |
| Pal | 2016 | Annals of Indian Academy of Neurology | FTLD patients included in patient group |
| Parnetti | 2011 | Movement Disorders | FTLD patients included in patient group |
| Pereira | 2009 | Neurology | FTLD patients included in patient group |
| Porto | 2008 | Dementia & Neuropsychologia | FTLD patients included in patient group |
| Rabinovici | 2008 | American Journal of Alzheimer's Disease & Other Dementias | FTLD patients included in patient group |
| Rabinovici | 2007 | Neurology | FTLD patients included in patient group |
| Rami | 2007 | Journal of Neurology | FTLD patients included in patient group |
| Rami | 2008 | Dementia & Geriatric Cognitive Disorders | FTLD patients included in patient group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Repetto | 2008 | Studies in Health Technology & Informatics | FTLD patients included in patient group |
| Santos | 2014 | Progress in Neuro-psychopharmacology & Biological Psychiatry | FTLD patients included in patient group |
| Schoonenboom | 2005 | Clinical Chemistry | FTLD patients included in patient group |
| Seripa | 2011 | Archives of Neurology | FTLD patients included in patient group |
| Seripa | 2012 | Journal of Alzheimer's Disease | FTLD patients included in patient group |
| Serrani | 2013 | Neurologia | FTLD patients included in patient group |
| Shigenobu | 2002 | Psychiatry Research | FTLD patients included in patient group |
| Soderlund | 2008 | Neuropsychologia | FTLD patients included in patient group |
| Sturm | 2006 | Brain | FTLD patients included in patient group |
| Sturm | 2015 | Cortex | FTLD patients included in patient group |
| Sturm | 2008 | Emotion | FTLD patients included in patient group |
| Suarez-Calvet | 2014 | Journal of Neurology, Neurosurgery and Psychiatry | FTLD patients included in patient group |
| Tallberg | 2002 | Brain and Language | FTLD patients included in patient group |
| Tarawneh | 2011 | Annals of Neurology | FTLD patients included in patient group |
| Troiani | 2011 | Neuropsychology | FTLD patients included in patient group |
| Vignini | 2013 | Experimental Gerontology | FTLD patients included in patient group |
| Villemagne | 2011 | Journal of Nuclear Medicine | FTLD patients included in patient group |
| Warkentin | 1993 | Dementia | FTLD patients included in patient group |
| Weickert | 2013 | Cortex | FTLD patients included in patient group |
| Werner | 2007 | Neurology | FTLD patients included in patient group |
| Whitwell | 2007 | NeuroImage | FTLD patients included in patient group |
| Wolf | 2009 | Nervenartzt | FTLD patients included in patient group |
| Downey | 2014 | Journal of Neurology, Neurosurgery and Psychiatry | MND patients included in the FTD cohort |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Lee | 2014 | Brain | MND patients included in the FTD cohort |
| Mansoor | 2015 | Alzheimer Disease & Associated Disorders | MND patients included in the FTD cohort |
| Adenzato | 2010 | Neuropsychologia | No (standardised) neuropsychological tests |
| Ahmed | 2017 | Brain | No (standardised) neuropsychological tests |
| Ahmed | 2016 | Journal of Neurology | No (standardised) neuropsychological tests |
| Ahmed | 2015 | Neurology | No (standardised) neuropsychological tests |
| Alberici | 2008 | Acta Neurol Scand | No (standardised) neuropsychological tests |
| Alcolea | 2017 | Neurology | No (standardised) neuropsychological tests |
| Ambikairajah | 2014 | Amyotrophic Lateral sclerosis & Frontotemporal Degeneration | No (standardised) neuropsychological tests |
| Antoine | 2005 | Revue de Geriatrie | No (standardised) neuropsychological tests |
| Arroyo-Anllo | 2015 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Arroyo-Anllo | 2017 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Avants | 2014 | NeuroImage | No (standardised) neuropsychological tests |
| Baez | 2014 | JAMA Neurology | No (standardised) neuropsychological tests |
| Baez | 2016 | Neurodegenerative Disease | No (standardised) neuropsychological tests |
| Bak | 2007 | Practical Neurology | No (standardised) neuropsychological tests |
| Balasa | 2015 | Neuropathology & Applied Neurobiology | No (standardised) neuropsychological tests |
| Baldock | 2014 | Archives of Clinical Neuropsychology | No (standardised) neuropsychological tests |
| Behrouzi | 2016 | Acta Neuropathologica | No (standardised) neuropsychological tests |
| Bertoux | 2015 | Frontiers in Neurology | No (standardised) neuropsychological tests |
| Bertoux | 2016 | Neurology | No (standardised) neuropsychological tests |
| Bibl | 2012 | Journal of Neural Transmission | No (standardised) neuropsychological tests |
| Bickart | 2014 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Bickart | 2014 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |
| Bisbing | 2015 | Frontiers in Human Neuroscience | No (standardised) neuropsychological tests |
| Blair | 2016 | Canadian Journal of Neurological Sciences | No (standardised) neuropsychological tests |
| Bochetta | 2016 | NeuroImage | No (standardised) neuropsychological tests |
| Bonakis | 2014 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Borroni | 2008 | Neurogenetics | No (standardised) neuropsychological tests |
| Borroni | 2010 | Rejuvenation Research | No (standardised) neuropsychological tests |
| Boxer | 2006 | Journal of Neuroscience | No (standardised) neuropsychological tests |
| Brodaty | 2015 | Journal of the American Medical Directors Association | No (standardised) neuropsychological tests |
| Bron | 2017 | Europian Radiology | No (standardised) neuropsychological tests |
| Brun | 1994 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |
| Busse | 2017 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Caixeta | 2015 | Clinical Practice & Epidemiology in Mental Health | No (standardised) neuropsychological tests |
| Carecchio | 2011 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Cecchini | 2017 | Journal of Neurology | No (standardised) neuropsychological tests |
| Chao | 2007 | Archives of Neurology | No (standardised) neuropsychological tests |
| Chen | 2015 | Journal of the Neurological Sciences | No (standardised) neuropsychological tests |
| Chen | 2016 | Psychiatric Genetics | No (standardised) neuropsychological tests |
| Chen | 2009 | Psychiatry Research | No (standardised) neuropsychological tests |
| Chiu | 2016 | American Journal of Geriatric Psychiatry | No (standardised) neuropsychological tests |
| Coleman | 2017 | Dementia & Geriatric Cognitive Disorders | No (standardised) neuropsychological tests |
| Cotelli | 2007 | Neuropsychologia | No (standardised) neuropsychological tests |
| Cotelli | 2006 | Neuropsychology | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Cova | 2012 | Consciousness and Cognition | No (standardised) neuropsychological tests |
| Cui | 2016 | Chinese Medical Journal | No (standardised) neuropsychological tests |
| Daianu | 2016 | Brain Imaging & Behavior | No (standardised) neuropsychological tests |
| Daianu | 2016 | Human Brain Mapping | No (standardised) neuropsychological tests |
| Dakson | 2011 | Acta Neuropathologica | No (standardised) neuropsychological tests |
| de Lopez | 2008 | Biological Psychiatry | No (standardised) neuropsychological tests |
| Della Rosa | 2014 | Neuroinformatics | No (standardised) neuropsychological tests |
| Deutsch | 2016 | International Psychogeriatrics | No (standardised) neuropsychological tests |
| Devenney | 2014 | JAMA Neurology | No (standardised) neuropsychological tests |
| Devenny | 2014 | JAMA Neurology | No (standardised) neuropsychological tests |
| Dietz | 2017 | Zeitschrift fur Gerontologie und Geriatrie | No (standardised) neuropsychological tests |
| Dimitrov | 2003 | Brain and Cognition | No (standardised) neuropsychological tests |
| Ehrlé | 2011 | Geriatrie Et Psychologie Neuropsychiatrie Du Vieillissement | No (standardised) neuropsychological tests |
| Elahi | 2017 | NeuroImage: clinical | No (standardised) neuropsychological tests |
| Elamin | 2016 | Dementia & Geriatric Cognitive Disorders | No (standardised) neuropsychological tests |
| Farag | 2010 | Cerebral Cortex | No (standardised) neuropsychological tests |
| Farb | 2013 | Cortex | No (standardised) neuropsychological tests |
| Fernandez Matarrubia | 2017 | International Journal of Geriatric Psychiatry | No (standardised) neuropsychological tests |
| Ferrari | 2016 | Europian Radiology | No (standardised) neuropsychological tests |
| Ferrari | 2017 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Fiandaca | 2015 | Alzheimer's & Dementia | No (standardised) neuropsychological tests |
| Filippi | 2013 | The Lancet Neurology | No (standardised) neuropsychological tests |
| Fiorentino | 2013 | Dementia & Neuropsychologia | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Fong | 2017 | Cortex | No (standardised) neuropsychological tests |
| Fong | 2017 | Social Neuroscience | No (standardised) neuropsychological tests |
| Forstl | 1996 | Dementia | No (standardised) neuropsychological tests |
| Freitas | 2012 | Journal of Geriatric Psychiatry | No (standardised) neuropsychological tests |
| Frings | 2014 | PLoS ONE | No (standardised) neuropsychological tests |
| Frings | 2014 | PLoS ONE | No (standardised) neuropsychological tests |
| Galimberti | 2013 | Biological Psychiatry | No (standardised) neuropsychological tests |
| Garraux | 1998 | NeuroImage | No (standardised) neuropsychological tests |
| Golimstok | 2014 | Translational Neurodegeneration | No (standardised) neuropsychological tests |
| Goodkind | 2015 | Emotion | No (standardised) neuropsychological tests |
| Goossens | 2017 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Grafman | 1999 | Lancet | No (standardised) neuropsychological tests |
| Gunawardena | 2010 | Neurology | No (standardised) neuropsychological tests |
| Halabi | 2013 | Alzheimer Disease & Associated Disorders | No (standardised) neuropsychological tests |
| Halpern | 2013 | Psychology of Aesthetics, Creativity, and the Arts | No (standardised) neuropsychological tests |
| Henry | 2014 | Neuropsychologia | No (standardised) neuropsychological tests |
| Hsieh | 2015 | Dementia & Geriatric Cognitive Disorders | No (standardised) neuropsychological tests |
| Iavarone | 2004 | Functional Neurology | No (standardised) neuropsychological tests |
| Ibanez | 2013 | Cognitive Neuroscience | No (standardised) neuropsychological tests |
| Johnen | 2015 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |
| Jonker | 1991 | Nederlands Tijdschrift voor Geneeskunde | No (standardised) neuropsychological tests |
| Josephs | 2015 | Lancet Neurology | No (standardised) neuropsychological tests |
| Josephs | 2008 | Neurobiology of Aging | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Joshi | 2014 | The Journal of Neuropsychiatry and Clinical Neurosciences | No (standardised) neuropsychological tests |
| Joshi | 2017 | The Journal of Neuropsychiatry and Clinical Neurosciences | No (standardised) neuropsychological tests |
| Joshi | 2014 | The Journal of neuropsychiatry and clinical neurosciences | No (standardised) neuropsychological tests |
| Kim | 2002 | Neuroscience Letters | No (standardised) neuropsychological tests |
| Kipps | 2008 | Neurology | No (standardised) neuropsychological tests |
| Laisney | 2011 | Revue de Neuropsychologie, Neurosciences Cognitives et Cliniques | No (standardised) neuropsychological tests |
| Lam | 2014 | Human Brain Mapping | No (standardised) neuropsychological tests |
| Larner | 2016 | The Journal of the Royal College of Physicians of Edinburgh | No (standardised) neuropsychological tests |
| Leuzy | 2016 | Brain Structure and Function | No (standardised) neuropsychological tests |
| Libon | 2011 | The Clinical Neuropsychologist | No (standardised) neuropsychological tests |
| Lima-Silva | 2013 | Dementia & Neuropsychologia | No (standardised) neuropsychological tests |
| Lista | 2017 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Lista | 2017 | Neurochemistry International | No (standardised) neuropsychological tests |
| Looi | 2012 | Australian & New Zealand Journal of Psychiatry | No (standardised) neuropsychological tests |
| Lopez-Gonzalez | 2016 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Lu | 2014 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Luis | 2016 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Magdalinou | 2015 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |
| Maserati | 2015 | Behavioural Neurology | No (standardised) neuropsychological tests |
| Massimo | 2015 | Frontiers in Human Neuroscience | No (standardised) neuropsychological tests |
| McMillan | 2013 | Frontiers in Psychology | No (standardised) neuropsychological tests |
| Meeter | 2016 | Annals of Clinical and Translational Neurology | No (standardised) neuropsychological tests |
| Mendez | 2009 | American Journal of Alzheimer's Disease & Other Dementias | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Mendez | 2005 | Cognitive & Behavioral Neurology | No (standardised) neuropsychological tests |
| Millenaar | 2017 | Aging & Mental Health | No (standardised) neuropsychological tests |
| Morenas-Rodriguez | 2015 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Mosconi | 2008 | The Journal of Nuclear Medicine | No (standardised) neuropsychological tests |
| Nishida | 2011 | Clinical Neurophysiology | No (standardised) neuropsychological tests |
| Ohta | 2017 | Journal of the Neurological Sciences | No (standardised) neuropsychological tests |
| Omer | 2017 | Amyotrophic Lateral sclerosis & Frontotemporal Degeneration | No (standardised) neuropsychological tests |
| Palumbo | 2014 | Open Nuclear Medicine Journal | No (standardised) neuropsychological tests |
| Pasquier | 2001 | Neurocase | No (standardised) neuropsychological tests |
| Perani | 2014 | NeuroImage: clinical | No (standardised) neuropsychological tests |
| Perneczky | 2007 | The European Journal of Nuclear Medicine and Molecular Imaging | No (standardised) neuropsychological tests |
| Perri | 2013 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Pijnenburg | 2015 | Alzheimer's & Dementia: diagnosis, assessment & disease monitoring | No (standardised) neuropsychological tests |
| Pressman | 2017 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |
| Rankin | 2008 | Journal of Clinical Psychiatry | No (standardised) neuropsychological tests |
| Rogalski | 2008 | Archives of Neurology | No (standardised) neuropsychological tests |
| Rosenberg | 2002 | Journal of the American Medical Association | No (standardised) neuropsychological tests |
| Rubinsztein | 2016 | Nature Medicine | No (standardised) neuropsychological tests |
| Sawrie | 1999 | The Journals of Gerontology | No (standardised) neuropsychological tests |
| Schanz | 2016 | Muscle Nerve | No (standardised) neuropsychological tests |
| Schirinzi | 2017 | Journal of Neural Transmission | No (standardised) neuropsychological tests |
| Schroeter | 2014 | Cortex | No (standardised) neuropsychological tests |
| Schroeter | 2014 | Cortex | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Shams | 2017 | American Journal of Neuroradiology | No (standardised) neuropsychological tests |
| Shany-Ur | 2014 | Brain | No (standardised) neuropsychological tests |
| Shdo | 2017 | Neuropsychologia | No (standardised) neuropsychological tests |
| Sheelakumari | 2017 | American Journal of Neuroradiology | No (standardised) neuropsychological tests |
| Skillback | 2014 | Neurology | No (standardised) neuropsychological tests |
| Sollbergeer | 2014 | Brain and Behavior | No (standardised) neuropsychological tests |
| Souliez | 1996 | Cortex | No (standardised) neuropsychological tests |
| Spotorno | 2015 | Neuropsychologia | No (standardised) neuropsychological tests |
| St. Jacques | 2015 | Neurocase | No (standardised) neuropsychological tests |
| Stefani | 2015 | Frontiers in Aging Neuroscience | No (standardised) neuropsychological tests |
| Steketee | 2016 | Neurobiology of Aging | No (standardised) neuropsychological tests |
| Strenziok | 2011 | Cognitive & Behavioral Neurology | No (standardised) neuropsychological tests |
| Strohminger | 2015 | Psychological Science | No (standardised) neuropsychological tests |
| Struhal | 2014 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Struyfs | 2015 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Sturm | 2011 | Scan | No (standardised) neuropsychological tests |
| Tan | 2014 | Brain | No (standardised) neuropsychological tests |
| Tan | 2014 | Brain | No (standardised) neuropsychological tests |
| Tan | 2014 | PLoS ONE | No (standardised) neuropsychological tests |
| Teunissen | 2016 | Alzheimer's & Dementia: diagnosis, assessment & disease monitoring | No (standardised) neuropsychological tests |
| Toledo | 2013 | Brain | No (standardised) neuropsychological tests |
| Torralva | 2009 | Journal of the International Neuropsychological Society | No (standardised) neuropsychological tests |
| Torrente | 2014 | Alzheimer Disease & Associated Disorders | No (standardised) neuropsychological tests |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Tosun | 2012 | NeuroImage | No (standardised) neuropsychological tests |
| Tovar-Moll | 2014 | PLoS ONE | No (standardised) neuropsychological tests |
| Tuovinen | 2017 | Frontiers in Human Neuroscience | No (standardised) neuropsychological tests |
| van den Stock | 2017 | Cortex | No (standardised) neuropsychological tests |
| van Kooten | 2015 | BMC Geriatrics | No (standardised) neuropsychological tests |
| Verfaillie | 2015 | Europian Radiology | No (standardised) neuropsychological tests |
| Walterfang | 2014 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Wellington | 2016 | Neurology | No (standardised) neuropsychological tests |
| Whitwell | 2016 | JAMA Neurology | No (standardised) neuropsychological tests |
| Whitwell | 2010 | Neurology | No (standardised) neuropsychological tests |
| Williamson | 2010 | Journal of Neurology, Neurosurgery and Psychiatry | No (standardised) neuropsychological tests |
| Woolley | 2014 | Neurology | No (standardised) neuropsychological tests |
| Yang | 2017 | Nature Scientific Reports | No (standardised) neuropsychological tests |
| Yunusova | 2016 | PLoS ONE | No (standardised) neuropsychological tests |
| Zakzanis | 1998 | Neuropsychiatry, Neuropsychology and Behavioral Neurology | No (standardised) neuropsychological tests |
| Zhang | 2012 | Journal of Alzheimer's Disease | No (standardised) neuropsychological tests |
| Zintl | 2009 | American Journal of Alzheimer's Disease & Other Dementias | No (standardised) neuropsychological tests |
| Zintl | 2010 | Nervenarzt | No (standardised) neuropsychological tests |
| Belderbos | 2003 | International Journal of Geriatric Psychiatry | No FTD patients included |
| Dopper | 2013 | Neurology | No FTD patients included |
| Falquez | 2015 | Neurorehabilitation | No FTD patients included |
| Klimkowicz | 2016 | Journal of the American Geriatrics Society | No FTD patients included |
| Lamm | 2005 | Cognitive Brain Research | No FTD patients included |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Lavoie | 2005 | Experimental Aging Research | No FTD patients included |
| MacPherson | 2014 | PLoS ONE | No FTD patients included |
| Morbelli | 2016 | European Journal of Nuclear Medicine & Molecular Imaging | No FTD patients included |
| Moreno | 2013 | Neurobiology of Aging | No FTD patients included |
| Amanzio | 2016 | Experimental Gerontology | No neuropsychological tests administered to control group |
| Aswathy | 2013 | Neurobiology of Aging | No neuropsychological tests administered to control group |
| Bertoux | 2016 | Journal of Neurology, Neurosurgery and Psychiatry | No neuropsychological tests administered to control group |
| Bonvicini | 2014 | Neurobiology of Aging | No neuropsychological tests administered to control group |
| Boone | 1999 | Journal of the International Neuropsychological Society | No neuropsychological tests administered to control group |
| Borroni | 2007 | Archives of Neurology | No neuropsychological tests administered to control group |
| Borroni | 2007 | BMC Neurology | No neuropsychological tests administered to control group |
| Boutoleau | 2016 | Neuropsychologia | No neuropsychological tests administered to control group |
| Cappelletti | 2012 | Neuropsychology | No neuropsychological tests administered to control group |
| Carlino | 2010 | Pain | No neuropsychological tests administered to control group |
| Clement | 2003 | Psychologie & Neuropsychiatrie du Vieillissement | No neuropsychological tests administered to control group |
| Coulthard | 2006 | Journal of Neurology | No neuropsychological tests administered to control group |
| Cousins | 2016 | Neuropsychologia | No neuropsychological tests administered to control group |
| Della Sala | 2012 | Neuropsychologia | No neuropsychological tests administered to control group |
| Di Lazzaro | 2006 | Neurology | No neuropsychological tests administered to control group |
| Diehl | 2004 | Neurobiology of Aging | No neuropsychological tests administered to control group |
| Dimitrov | 1996 | Cortex | No neuropsychological tests administered to control group |
| Engelborghs | 2006 | Neurochemistry International | No neuropsychological tests administered to control group |
| Frings | 2010 | Dementia & Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Garibotto | 2011 | Neurobiology of Aging | No neuropsychological tests administered to control group |
| Green | 1999 | Neuroscience Letters | No neuropsychological tests administered to control group |
| Grimmer | 2004 | Dementia & Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |
| Guedj | 2007 | Neurology | No neuropsychological tests administered to control group |
| Healey | 2015 | Neuropsychologia | No neuropsychological tests administered to control group |
| Hensel | 2004 | Dementia & Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |
| Hu | 2010 | Neurology | No neuropsychological tests administered to control group |
| Hughes | 2011 | Brain | No neuropsychological tests administered to control group |
| Kaufer | 1997 | Neurology | No neuropsychological tests administered to control group |
| Kipps | 2007 | Dementia and Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |
| Krueger | 2007 | Neurocase | No neuropsychological tests administered to control group |
| Lindau | 2003 | Dementia & Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |
| Liu | 2004 | Neurology | No neuropsychological tests administered to control group |
| Luzzi | 2011 | Journal of Neurology | No neuropsychological tests administered to control group |
| Mahoney | 2012 | Alzheimer's Research & Therapy | No neuropsychological tests administered to control group |
| McMillan | 2012 | Neurology | No neuropsychological tests administered to control group |
| Mecocci | 1998 | Alzheimer Disease & Associated Disorders | No neuropsychological tests administered to control group |
| Mendez | 2014 | American Journal of Alzheimer's Disease & Other Dementias | No neuropsychological tests administered to control group |
| Meyniel | 2005 | Journal of Neurology | No neuropsychological tests administered to control group |
| Nakano | 2006 | NeuroImage | No neuropsychological tests administered to control group |
| Nevler | 2017 | Neurology | No neuropsychological tests administered to control group |
| Padovani | 2010 | Journal of Alzheimer's Disease | No neuropsychological tests administered to control group |
| Paholpak | 2016 | Journal of Alzheimer's Disease | No neuropsychological tests administered to control group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Pakhomov | 2010 | Journal of Neurolinguistics | No neuropsychological tests administered to control group |
| Pardini | 2009 | Archives of Neurology | No neuropsychological tests administered to control group |
| Pasquier | 1995 | Journal of Neurology | No neuropsychological tests administered to control group |
| Pawlowski | 2017 | Neurobiology of Aging | No neuropsychological tests administered to control group |
| Perry | 2006 | Dementia and Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |
| Peters | 2006 | Dementia & Geriatric Cognitive Disorders | No neuropsychological tests administered to control group |
| Pierantozzi | 2004 | Clinical Neurophysiology | No neuropsychological tests administered to control group |
| Placek | 2016 | Neurology | No neuropsychological tests administered to control group |
| Raczka | 2010 | Psychiatry Research | No neuropsychological tests administered to control group |
| Rucco | 2017 | Gait & Posture | No neuropsychological tests administered to control group |
| Santamaria-Garcia | 2016 | Journal of Alzheimer's Disease | No neuropsychological tests administered to control group |
| Spotorno | 2015 | Frontiers in Human Neuroscience | No neuropsychological tests administered to control group |
| Tovar-Moll | 2014 | PLoS ONE | No neuropsychological tests administered to control group |
| Trojsi | 2015 | Neurobiology of Aging | No neuropsychological tests administered to control group |
| Vartanian | 2009 | Neuropsychology | No neuropsychological tests administered to control group |
| Zamboni | 2008 | Neurology | No neuropsychological tests administered to control group |
| Barekatain | 2010 | Dementia & Geriatric Cognitive Disorders | Other types of dementia included in patient group |
| Beversdorf | 1998 | Neurology | Other types of dementia included in patient group |
| Cavallo | 2011 | Acta Neuropsychologica | Other types of dementia included in patient group |
| Chase | 1987 | Archives of Gerontology & Geriatrics | Other types of dementia included in patient group |
| Choi | 2000 | Journal of Korean Medical Science | Other types of dementia included in patient group |
| Crookes | 1972 | British Journal of Social & Clinical Psychology | Other types of dementia included in patient group |
| Diesfeldt | 2009 | Tijdschrift voor Gerontologie en Geriatrie | Other types of dementia included in patient group |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Eslinger | 1983 | Journal of Clinical Neuropsychology | Other types of dementia included in patient group |
| Foster | 1989 | Progress in Neuro-Psychopharmacology & Biological Psychiatry | Other types of dementia included in patient group |
| Garcia-Caballero | 2006 | International Journal of Geriatric Psychiatry | Other types of dementia included in patient group |
| Gee | 2003 | Academic Radiology | Other types of dementia included in patient group |
| Guaita | 2009 | Archives of Gerontology & Geriatrics | Other types of dementia included in patient group |
| Hagberg | 1976 | British Journal of Psychiatry | Other types of dementia included in patient group |
| Hanyu | 2002 | American Journal of Neuroradiology | Other types of dementia included in patient group |
| Hart | 2006 | Aging, Neuropsychology, and Cognition | Other types of dementia included in patient group |
| Ideno | 2012 | Geriatrics & Gerontology International | Other types of dementia included in patient group |
| Iype | 2006 | Journal of Neurology, Neurosurgery and Psychiatry | Other types of dementia included in patient group |
| Miller | 1971 | Neuropsychologia | Other types of dementia included in patient group |
| Mioshi | 2006 | International Journal of Geriatric Psychiatry | Other types of dementia included in patient group |
| Pasquier | 1997 | Journal of Neurology | Other types of dementia included in patient group |
| Persson | 2017 | Acta Radiologica | Other types of dementia included in patient group |
| Sells | 2011 | Progress in Neurology and Psychiatry | Other types of dementia included in patient group |
| Torrisi | 2017 | Psychogeriatrics | Other types of dementia included in patient group |
| Uhlhaas | 2008 | Dementia & Geriatric Cognitive Disorders | Other types of dementia included in patient group |
| Vogel | 2014 | Dementia & Geriatric Cognitive Disorders | Other types of dementia included in patient group |
| Wahlund | 2000 | Journal of Neurology | Other types of dementia included in patient group |
| Whitwell | 2009 | Neurology | Other types of dementia included in patient group |
| Woolley | 2007 | Neurology | Other types of dementia included in patient group |
| Xu | 2017 | International Journal of Neuroscience | Other types of dementia included in patient group |
| Krueger | 2009 | Neurology | Patient selection based on performance |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Arevalorodriguez | 2015 | Advances in Psychiatric Treatment | Review |
| Arevalorodriguez | 2015 | The British Journal of Psychiatry Advances | Review |
| Hafkemeijer | 2016 | Human Brain Mapping | Same patient group as Hafkemeijer 2015 |
| Nishida | 2013 | Clinical Neurophysiology | Same patient group as Nishidi 2011 |
| Gleichgerrcht | 2010 | Journal of the International Neuropsychological Society | Same patient group as Torralva 2009 |
| Adler | 2003 | International Journal of Geriatric Psychiatry | Uncontrolled study |
| Anterion | 2002 | Neurology | Uncontrolled study |
| Arzy | 2008 | Neurology | Uncontrolled study |
| Avants | 2005 | Alzheimer Disease & Associated Disorders | Uncontrolled study |
| Banks | 2009 | Journal of Neuropsychiatry & Clinical Neurosciences | Uncontrolled study |
| Beck | 2014 | International Journal of Geriatric Psychiatry | Uncontrolled study |
| Bibl | 2011 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |
| Blair | 2007 | Journal of the International Neuropsychological Society | Uncontrolled study |
| Borroni | 2010 | American Journal of Geriatric Psychiatry | Uncontrolled study |
| Borroni | 2010 | European Journal of Neurology | Uncontrolled study |
| Boutoleau-Bretonniere | 2012 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |
| Braaten | 2006 | International Journal of Neuroscience | Uncontrolled study |
| Buhl | 2013 | Dementia and Geriatric Cognitive Disorders | Uncontrolled study |
| Caso | 2012 | Neurobiology of Aging | Uncontrolled study |
| Chan | 2014 | Australian & New Zealand Journal of Psychiatry | Uncontrolled study |
| Charpentier | 2000 | Journal of Neurology | Uncontrolled study |
| Chiu | 2006 | Journal of the Formosan Medical Association | Uncontrolled study |
| Chow | 2006 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |





**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Das | 2009 | NeuroImage | Uncontrolled study |
| Degerman Gunnarsson | 2013 | Dementia and Geriatric Cognitive Disorders | Uncontrolled study |
| Diehl | 2011 | International Psychogeriatrics | Uncontrolled study |
| Diehl | 2005 | Journal of Geriatric Psychiatry & Neurology | Uncontrolled study |
| Downey | 2012 | Alzheimer's Research & Therapy | Uncontrolled study |
| Elfgren | 1993 | Dementia | Uncontrolled study |
| Engelborghs | 2005 | International Journal of Geriatric Psychiatry | Uncontrolled study |
| Engelborghs | 2008 | Neurochemistry International | Uncontrolled study |
| Engelborghs | 2004 | International Journal of Geriatric Psychiatry | Uncontrolled study |
| Franceschi | 2011 | Behavioural Neurology | Uncontrolled study |
| Fukui | 2000 | Journal of the Neurological Sciences | Uncontrolled study |
| Gabelle | 2011 | Journal of Alzheimer's Disease | Uncontrolled study |
| Gansler | 2017 | Journal of Neurology, Neurosurgery and Psychiatry | Uncontrolled study |
| Garn | 2017 | Journal of Neural Transmission | Uncontrolled study |
| Garraux | 1999 | Journal of the Neurological Sciences | Uncontrolled study |
| Gasparini | 2008 | European Journal of Neurology | Uncontrolled study |
| Gleichgerrcht | 2011 | Social Neuroscience | Uncontrolled study |
| Glosser | 2002 | Neuropsychology | Uncontrolled study |
| Grossman | 2004 | Brain and Language | Uncontrolled study |
| Grossman | 1998 | Neurology | Uncontrolled study |
| Gustafson | 1978 | Brain and Language | Uncontrolled study |
| Haanpaa | 2015 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Hornberger | 2014 | Human Brain Mapping | Uncontrolled study |
| Hornberger | 2014 | Human Brain Mapping | Uncontrolled study |
| Hsieh | 2016 | Journal of Alzheimer's Disease | Uncontrolled study |
| Irwin | 2013 | Journal of Neurology, Neurosurgery and Psychiatry | Uncontrolled study |
| Kaiser | 2013 | Neuropsychologia | Uncontrolled study |
| Kim | 2014 | Dementia and Geriatric Cognitive Disorders | Uncontrolled study |
| Kurisu | 2016 | International Psychogeriatrics | Uncontrolled study |
| Larner | 2010 | Age & Ageing | Uncontrolled study |
| Lavenu | 2005 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |
| Le Ber | 2006 | Brain | Uncontrolled study |
| Le Ber | 2013 | JAMA Neurology | Uncontrolled study |
| Lima-Silva | 2013 | Dementia & Neuropsychologia | Uncontrolled study |
| Lindberg | 2012 | Frontiers in Aging Neuroscience | Uncontrolled study |
| Liu | 2017 | Aging & Mental Health | Uncontrolled study |
| Lu | 2014 | Journal of Alzheimer's Disease | Uncontrolled study |
| Maeshima | 2004 | Brain Injury | Uncontrolled study |
| Maiovis | 2017 | The Journal of Neuropsychiatry and Clinical Neurosciences | Uncontrolled study |
| Matsuzono | 2015 | Journal of Alzheimer's Disease | Uncontrolled study |
| Mendez | 2008 | International Journal of Geriatric Psychiatry | Uncontrolled study |
| Mendez | 1996 | Neurology | Uncontrolled study |
| Mendez | 2015 | PLoS ONE | Uncontrolled study |
| Miller | 2013 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |
| Moheb | 2017 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study |

**Table e-4.** Continued.

| | | | |
|---|---|---|---|
| Narme | 2017 | Aging, Neuropsychology, and Cognition | Uncontrolled study |
| Padovani | 2013 | Journal of Alzheimer's Disease | Uncontrolled study |
| Palumbo | 2014 | The Open Nuclear Medicine Journal | Uncontrolled study |
| Park | 2017 | Australasian Journal of Ageing | Uncontrolled study |
| Paternico | 2016 | Nature Scientific Reports | Uncontrolled study |
| Paternico | 2015 | Neurology | Uncontrolled study |
| Perini | 2016 | Alzheimer Disease & Associated Disorders | Uncontrolled study |
| Perri | 2014 | Journal of Alzheimer's Disease | Uncontrolled study |
| Perri | 2014 | Journal of Alzheimer's Disease | Uncontrolled study |
| Pickut | 1997 | Journal of Nuclear Medicine | Uncontrolled study |
| Poletti | 2013 | Neurological Sciences | Uncontrolled study |
| Powers | 2014 | Cognitive & Behavioral Neurology | Uncontrolled study |
| Premi | 2016 | Journal of Alzheimer's Disease | Uncontrolled study |
| Premi | 2015 | Neurobiology of Aging | Uncontrolled study |
| Ramanan | 2017 | Cortex | Uncontrolled study |
| Rentzos | 2006 | Journal of the Neurological Sciences | Uncontrolled study |
| Ritter | 2017 | Alzheimer Disease & Associated Disorders | Uncontrolled study |
| Roncero | 2017 | Alzheimer's & Dementia: translational research & clinical interventions | Uncontrolled study |
| Saxon | 2017 | Journal of Neurology, Neurosurgery and Psychiatry | Uncontrolled study |
| Shea | 2015 | Psychogeriatrics | Uncontrolled study |
| Shimomura | 1998 | Lancet | Uncontrolled study |
| Simonsen | 2014 | Dementia and Geriatric Cognitive Disorders | Uncontrolled study |
| Suhonen | 2017 | Journal of Alzheimer's Disease | Uncontrolled study |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suhonen | 2017 | Journal of Alzheimer's Disease | Uncontrolled study | | | | | | | | | | | | | | | |
| Tan | 2013 | Alzheimer Disease & Associated Disorders | Uncontrolled study | | | | | | | | | | | | | | | |
| Torralva | 2015 | Neurobiology of Aging | Uncontrolled study | | | | | | | | | | | | | | | |
| Uflacker | 2016 | International Psychogeriatrics | Uncontrolled study | | | | | | | | | | | | | | | |
| Valotassiou | 2014 | Current Alzheimer Research | Uncontrolled study | | | | | | | | | | | | | | | |
| van den Berg | 2017 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study | | | | | | | | | | | | | | | |
| Van Langenhove | 2016 | Journal of Alzheimer's Disease | Uncontrolled study | | | | | | | | | | | | | | | |
| Vergallo | 2017 | Neurological Sciences | Uncontrolled study | | | | | | | | | | | | | | | |
| Vieira | 2008 | Dementia & Neuropsychologia | Uncontrolled study | | | | | | | | | | | | | | | |
| Wang | 2016 | Translational Neuroscience | Uncontrolled study | | | | | | | | | | | | | | | |
| Wetherell | 1997 | International Journal of Rehabilitation and Health | Uncontrolled study | | | | | | | | | | | | | | | |
| Whitwell | 2015 | European Journal of Neurology | Uncontrolled study | | | | | | | | | | | | | | | |
| Ye | 2015 | Journal of Alzheimer's Disease | Uncontrolled study | | | | | | | | | | | | | | | |
| Yoshizawa | 2013 | Dementia & Geriatric Cognitive Disorders | Uncontrolled study | | | | | | | | | | | | | | | |
| Yu | 2016 | Neurobiology of Aging | Uncontrolled study | | | | | | | | | | | | | | | |
| Larner | 2005 | International Journal of Geriatric Psychiatry | Uncontrolled study | | | | | | | | | | | | | | | |

**Table e-4.** Continued.





**Table e-5.** Subgroup analysis for age

| Cognitive domain | Age (years) | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| Social cognition | ≤ 64.0 | 1.87 | 1.49-2.24 | 24 | 941 | 0.76 | 0.38 | 0 |
| | > 64.0 | 1.66 | 1.41-1.92 | 16 | 695 | | | |
| Fluency | ≤ 64.0 | 1.65 | 1.52-1.78 | 34 | 1279 | 3.14 | 0.08 | 68.1 |
| | > 64.0 | 1.44 | 1.26-1.63 | 34 | 1464 | | | |
| Executive functions | ≤ 64.0 | 1.45 | 1.30-1.60 | 40 | 1502 | 0.26 | 0.61 | 0 |
| | > 64.0 | 1.39 | 1.20-1.57 | 41 | 1736 | | | |
| Verbal memory | ≤ 64.0 | 1.67 | 1.42-1.93 | 30 | 1038 | 0.00 | 0.97 | 0 |
| | > 64.0 | 1.68 | 1.46-1.90 | 26 | 984 | | | |
| Visual memory | ≤ 64.0 | 1.35 | 1.15-1.55 | 30 | 1052 | 0.07 | 0.80 | 0 |
| | > 64.0 | 1.31 | 1.04-1.57 | 21 | 771 | | | |
| Visuoconstruction | ≤ 64.0 | 0.90 | 0.65-1.15 | 16 | 633 | 1.52 | 0.22 | 34.1 |
| | > 64.0 | 1.16 | 0.83-1.50 | 8 | 371 | | | |
| Language | ≤ 64.0 | 1.22 | 1.08-1.36 | 35 | 1202 | 4.48 | 0.03 | 77.7 |
| | > 64.0 | 0.99 | 0.83-1.15 | 22 | 826 | | | |
| Psychomotor speed | ≤ 64.0 | 0.95 | 0.72-1.18 | 18 | 557 | 1.05 | 0.30 | 5.2 |
| | > 64.0 | 1.12 | 0.88-1.36 | 21 | 865 | | | |
| Attention | ≤ 64.0 | 1.06 | 0.91-1.22 | 32 | 1161 | 2.50 | 0.11 | 60.0 |
| | > 64.0 | 0.85 | 0.64-1.07 | 29 | 1293 | | | |
| Visuoperception | ≤ 64.0 | 0.68 | 0.47-0.89 | 11 | 348 | 0.39 | 0.53 | 0 |
| | > 64.0 | 0.78 | 0.53-1.04 | 8 | 315 | | | |

Legend. Subgroups are based on a median split of age across the included studies. Hedges' g: effect size, calculated with a random effects model; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q—degrees of freedom/Q×100%).

**Table e-6.** Subgroup analysis for disease duration

| Cognitive domain | Disease duration (years) | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| Social cognition | ≤ 4.2 | 2.04 | 1.33-2.75 | 9 | 430 | 0.63 | 0.43 | 0 |
| | > 4.2 | 1.66 | 1.05-2.27 | 9 | 282 | | | |
| Fluency | ≤ 4.2 | 1.63 | 1.42-1.87 | 17 | 781 | 0.02 | 0.90 | 0 |
| | > 4.2 | 1.64 | 1.45-1.80 | 18 | 666 | | | |
| Executive functions | ≤ 4.2 | 1.49 | 1.19-1.79 | 20 | 843 | 0.28 | 0.60 | 0 |
| | > 4.2 | 1.39 | 1.14-1.63 | 23 | 775 | | | |
| Verbal memory | ≤ 4.2 | 1.70 | 1.39-2.01 | 15 | 771 | 2.82 | 0.09 | 64.5 |
| | > 4.2 | 2.08 | 1.77-2.38 | 17 | 554 | | | |
| Visual memory | ≤ 4.2 | 1.36 | 0.90-1.83 | 12 | 476 | 0.20 | 0.66 | 0 |
| | > 4.2 | 1.48 | 1.30-1.65 | 22 | 746 | | | |
| Visuoconstruction | ≤ 4.2 | 1.48 | 1.06-1.90 | 5 | 192 | 7.76 | 0.005 | 87.1 |
| | > 4.2 | 0.75 | 0.45-1.05 | 8 | 257 | | | |

**Table e-6.** Continued.

| Cognitive domain | Disease duration (years) | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| Language | ≤ 4.2 | 1.25 | 0.97-1.53 | 13 | 521 | 0.08 | 0.77 | 0 |
| | > 4.2 | 1.20 | 1.02-1.38 | 24 | 802 | | | |
| Psychomotor speed | ≤ 4.2 | 0.86 | 0.64-1.09 | 9 | 330 | 1.74 | 0.19 | 42.5 |
| | > 4.2 | 1.17 | 0.77-1.56 | 12 | 396 | | | |
| Attention | ≤ 4.2 | 1.11 | 0.82-1.40 | 16 | 687 | 1.47 | 0.23 | 31.8 |
| | > 4.2 | 0.89 | 0.67-1.11 | 21 | 784 | | | |
| Visuoperception | ≤ 4.2 | 0.57 | 0.31-0.83 | 2 | 50 | 1.33 | 0.25 | 0 |
| | > 4.2 | 0.78 | 0.54-1.01 | 8 | 312 | | | |

Legend. Subgroups are based on a median split of disease duration (years) across the included studies. Hedges' g: effect size, calculated with a random effects model; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q—degrees of freedom/Q×100%).

**Table e-7.** Subgroup analysis for education

| Cognitive domain | Education (years) | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| Social cognition | ≤ 12.2 | 1.67 | 1.32-2.02 | 18 | 751 | 0.55 | 0.46 | 0 |
| | > 12.2 | 1.86 | 1.50-2.21 | 22 | 830 | | | |
| Fluency | ≤ 12.2 | 1.65 | 1.44-1.87 | 30 | 1188 | 1.77 | 0.18 | 43.4 |
| | > 12.2 | 1.48 | 1.35-1.61 | 33 | 1412 | | | |
| Executive functions | ≤ 12.2 | 1.49 | 1.26-1.71 | 34 | 1302 | 0.32 | 0.57 | 0 |
| | > 12.2 | 1.41 | 1.27-1.55 | 42 | 1717 | | | |
| Verbal memory | ≤ 12.2 | 1.78 | 1.52-2.05 | 25 | 981 | 0.74 | 0.39 | 0 |
| | > 12.2 | 1.62 | 1.37-1.87 | 23 | 862 | | | |
| Visual memory | ≤ 12.2 | 1.30 | 1.08-1.51 | 26 | 874 | 0.37 | 0.54 | 0 |
| | > 12.2 | 1.40 | 1.15-1.65 | 22 | 847 | | | |
| Visuoconstruction | ≤ 12.2 | 1.02 | 0.73-1.30 | 14 | 485 | 0.67 | 0.41 | 0 |
| | > 12.2 | 0.84 | 0.54-1.14 | 8 | 386 | | | |
| Language | ≤ 12.2 | 1.13 | 0.92-1.35 | 21 | 696 | 0.01 | 0.92 | 0 |
| | > 12.2 | 1.15 | 1.02-1.28 | 32 | 1222 | | | |
| Psychomotor speed | ≤ 12.2 | 1.11 | 0.89-1.33 | 17 | 607 | 0.35 | 0.55 | 0 |
| | > 12.2 | 1.00 | 0.73-1.27 | 19 | 711 | | | |
| Attention | ≤ 12.2 | 1.21 | 0.97-1.44 | 28 | 1140 | 6.72 | 0.01 | 85.1 |
| | > 12.2 | 0.83 | 0.66-0.99 | 28 | 1142 | | | |
| Visuoperception | ≤ 12.2 | 0.50 | 0.31-0.69 | 6 | 212 | 8.27 | 0.004 | 87.9 |
| | > 12.2 | 0.92 | 0.70-1.14 | 11 | 370 | | | |

Legend. Subgroups are based on a median split of years of education across the included studies. Hedges' g: effect size, calculated with a random effects model; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q—degrees of freedom/Q×100%).





**Table e-8.** Subgroup analysis for disease severity

| Cognitive domain | Disease severity | Hedges' g | 95% CI | K | N | Q | p (Q) | $I^2$ (%) |
|---|---|---|---|---|---|---|---|---|
| Social cognition | Mild | 1.49 | 1.09-1.88 | 11 | 403 | 2.77 | 0.10 | 63.9 |
| | Severe | 2.12 | 1.48-2.76 | 10 | 457 | | | |
| Fluency | Mild | 1.35 | 1.13-1.57 | 19 | 737 | 3.13 | 0.08 | 68.1 |
| | Severe | 1.60 | 1.43-1.78 | 20 | 814 | | | |
| Executive functions | Mild | 1.29 | 1.11-1.48 | 21 | 796 | 0.00 | 0.97 | 0 |
| | Severe | 1.29 | 1.04-1.53 | 23 | 958 | | | |
| Verbal memory | Mild | 1.40 | 1.05-1.75 | 14 | 491 | 5.12 | 0.02 | 80.5 |
| | Severe | 1.97 | 1.62-2.33 | 11 | 379 | | | |
| Visual memory | Mild | 1.24 | 0.96-1.52 | 14 | 515 | 0.88 | 0.35 | 0 |
| | Severe | 1.47 | 1.09-1.85 | 15 | 544 | | | |
| Visuoconstruction | Mild | 0.89 | 0.59-1.19 | 10 | 379 | 0.05 | 0.82 | 0 |
| | Severe | 1.00 | 0.14-1.85 | 4 | 121 | | | |
| Language | Mild | 1.03 | 0.87-1.18 | 18 | 661 | 2.77 | 0.10 | 63.9 |
| | Severe | 1.27 | 1.03-1.52 | 13 | 479 | | | |
| Psychomotor speed | Mild | 1.01 | 0.76-1.26 | 13 | 503 | 0.11 | 0.74 | 0 |
| | Severe | 0.94 | 0.62-1.26 | 8 | 245 | | | |
| Attention | Mild | 1.00 | 0.81-1.19 | 18 | 719 | 0.28 | 0.60 | 0 |
| | Severe | 1.10 | 0.80-1.40 | 15 | 587 | | | |
| Visuoperception | Mild | 0.66 | 0.44-0.87 | 4 | 136 | 0.33 | 0.56 | 0 |
| | Severe | 0.82 | 0.31-1.33 | 3 | 79 | | | |

Legend. Disease severity was measured with four scales and a median split was made across the included studies: Clinical Dementia Rating scale (CDR, split 1.1 ), CDR sum of boxes (split 6.1), Addenbrooke's Cognitive Examination – Revised (split 78.5) or the Mattis Dementia Rating Scale (split 126.0); Hedges' g: effect size, calculated with a random effects model; 95% CI: 95% confidence interval of effect size; K: number of studies; N: number of participants; Q: heterogeneity between studies within cognitive domain; p (Q): p value for heterogeneity; $I^2$: percentage of heterogeneity caused by study differences (Q—degrees of freedom/Q×100%).

# 4

## A systematic review of behavioural changes in motor neuron disease

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## ABSTRACT

### Objective
Motor neuron disease (MND) and the behavioural variant of frontotemporal dementia (bvFTD) are thought to be part of a disease spectrum. There is uncertainty about the frequency and characteristics of behavioural changes in MND, and similarly, about a relation between bvFTD and the site of onset of MND. Our aim was to perform a systematic review of the publications on behavioural changes in MND.

### Methods
An extensive search for articles on behavioural changes in MND patients was performed. First, cohort studies of MND patients were reviewed to summarize the prevalence of bvFTD and mild behavioural changes. Secondly, data on bvFTD symptoms (mostly from case reports) of individual MND-bvFTD patients were used to analyse characteristics and pooled prevalences of bvFTD symptoms. In addition, site of onset, survival and demographic variables of MND-bvFTD patients were analysed.

### Results
Results showed that in cohorts, 8.1% (95% CI 5.6 – 11.5%) of MND patients had bvFTD. In 170 individual patients with MND-bvFTD, perseveration (40%), apathy (29%) and disinhibition (26%) were the most frequently reported behavioural changes; 43% had memory disturbances and bulbar onset was found in 48%.

### Conclusion
In conclusion, 8% of MND patients have bvFTD, with perseveration being reported most frequently. MND-bvFTD is often accompanied by memory disturbances and is related to bulbar onset.






## INTRODUCTION

Neuropathological and genetic studies have suggested a disease spectrum with motor neuron disease (MND) and frontotemporal lobar degeneration (FTLD) on the extreme ends.[1, 2] This spectrum includes a variety of cognitive disturbances and behavioural symptoms in amyotrophic lateral sclerosis (ALS), the major form of MND. When these behavioural symptoms are severe, criteria for the behavioural variant of frontotemporal dementia (bvFTD) may be fulfilled.[3]

Neuropsychological studies have shown that cognitive deficits can be observed in 27 – 45% of ALS patients including impairments of executive, memory and language functions.[4-6] These findings, and the absence of visuospatial dysfunction[7], suggest a 'frontotemporal cognitive profile'.[8] Similar findings have been shown in patients with progressive muscular atrophy (PMA) and primary lateral sclerosis (PLS), the lower and upper motor neuron variants of MND, respectively.[7, 9]

The frequency and characteristics of behavioural symptoms however, which are the hallmark of bvFTD, have not been firmly determined in MND. There is ongoing debate about the prevalence of behavioural changes (both bvFTD and mild behavioural changes) and the association of bvFTD with clinical variables of MND, i.e. bulbar onset and survival.[10-13] Our aim was to systematically review the literature on MND and behaviour in order to 1) estimate the prevalence of bvFTD and of mild behavioural changes in MND; 2) calculate prevalence rates of bvFTD symptoms (behavioural, cognitive and psychiatric symptoms) in MND-bvFTD patients; and 3) determine the site of MND onset, survival and age of onset in MND-bvFTD patients.

## METHODS

### Literature search
A comprehensive literature search was conducted in October 2011 in PubMed (1954 – ), Web of Science (1975 – ) and PsycInfo (1860 – ) for articles in English, French, German, Italian and Dutch with the search terms in Box 1. The nomenclature of the entity now known as bvFTD has changed over time, and therefore patients with the diagnoses 'MND-Pick's disease, MND-dementia' were included in our search. Full-length articles, reviews and abstracts were considered. Articles were retrieved on MND patients with bvFTD on the one hand, and patients with dementia and MND symptoms on the other. Articles were screened by their title and, if judged possibly relevant, the abstract was

read. Relevant articles were evaluated in detail. Reference lists were checked for additional articles (Figure 1).

**Box 1 List of keywords**

MND related keywords:
Amyotrophic Lateral Sclerosis; ALS; Gehrig Disease; Gehrigs Disease; Gehrig's Disease; Lou Gehrig Disease; Lou Gehrigs Disease; Lou Gehrig's Disease; MND; Motor Neuron Disease; Motor Neurone Disease; amyotrophe Lateralsklerose; amyotrophieschen Lateralsklerose; amyotrophische Lateralsklerose; amyotrophischer Lateralsklerose; sclerose laterale amiotrofica; sclerose laterale amyotrophique; sclerosi laterale amiotrofica; SLA; Progressive muscular atrophy; Progressive Spinal Muscular Atrophy; PMA; PSMA, atrophie musculaire progressive, lower motor neuron disease, lower motoneuron disease, lower motor neurone disease, Primary Lateral Sclerosis; PLS, upper motor neuron disease, upper motoneuron disease, upper motor neurone disease (the search was repeated with 'disease' replaced by 'disorder' and 'syndrome').
*FTD related keywords:*
Behavior; Behavioral changes; Behaviour; Behavioural changes; Mild behavioural changes; Dementia; Frontal lobe dementia; Frontotemporal dementia; Frontotemporal Lobar Degeneration; Frontotemporal Lobar Degenerations; Frontotemporal lobe degeneration; FTD; FTLD; Pick Disease; Pick's disease; Picks Disease; Presenile dementia; Demence; Demence presenile; Demence progressive; disturbi mentali; disturbi psichici; les troubles mentaux; maladie de Pick; Pickse Krankheit; Psychiatrische Storungen; Psychiatrischen Storungen; Psychische Störung; Psychischen Symptomen.

**Inclusion and exclusion criteria**
Articles judged to be relevant were divided into cohort studies (part A) and case-studies/series (part B, Figure 1).

In part A of the study, the cohort studies were used to examine the prevalence of bvFTD and mild behavioural changes in MND.

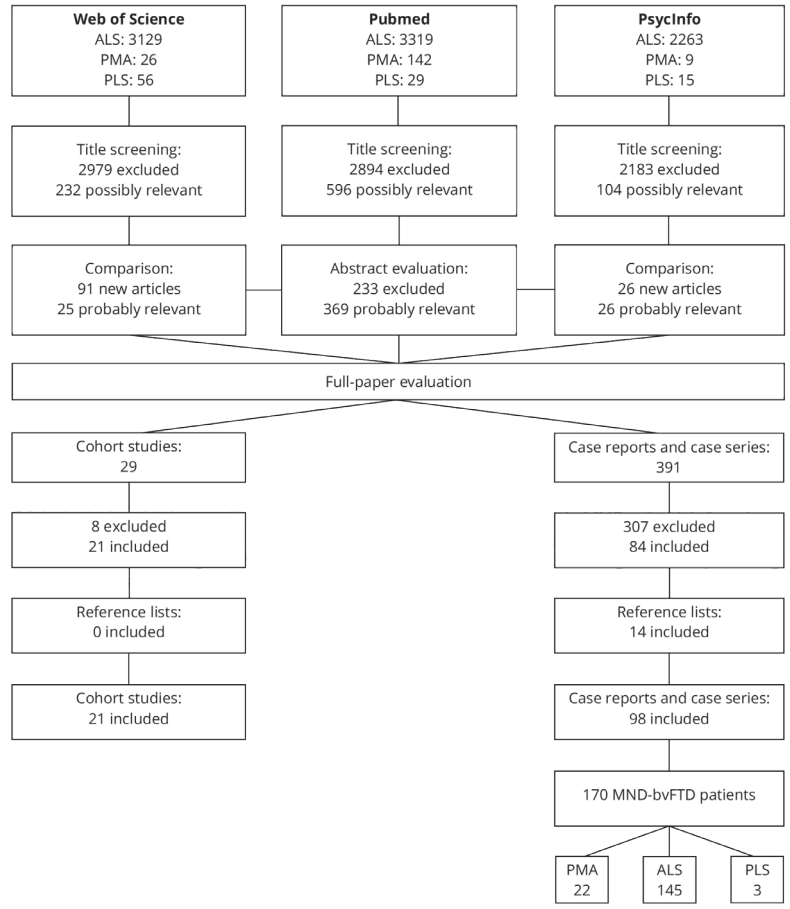
For part A of the study we included all prospective studies with an inception cohort if they reported:
- a description of the patient sample;
- a validated method to assess either FTD or mild behavioural changes;
- prevalence rates, or data enabling calculation of prevalence rates, of the behavioural subtype of frontotemporal dementia/frontotemporal lobar degeneration (FTLD) or mild behavioural changes.

For part B of the study, case reports and case series were used to calculate prevalence rates of bvFTD symptoms (behavioural, cognitive and psychiatric symptoms) in MND-bvFTD patients. In addition, within the group of MND-bvFTD patients we compared the site of onset, survival and age of onset between the MND onset and bvFTD-onset patients.





**Figure 1.** Search strategy and results




Of the 21 included cohort studies, nine calculated the prevalence of bvFTD in MND, of which four also determined the prevalence of mild behavioural changes in MND; four other studies calculated the prevalence of mild behavioural changes in MND and eight studies described behavioural changes without presenting prevalence rates.

For part B, single case studies, case series and reviews including one or more case studies of MND-bvFTD patients with either MND or bvFTD onset were included if they reported:
- bvFTD symptoms in one (single case study) or more (case series) individual patients;
- information allowing the extraction of
  - the diagnosis ALS, PMA or PLS;
  - one of the following diagnoses: FTD, Pick's disease, FTLD or ALS-dementia.

Studies were excluded for part B of the study if they reported:

- patients with pure language variants of FTLD (i.e. without behavioural changes) or Alzheimer's disease (i.e. a clinical and pathological diagnosis);
- patients with MND variants (e.g. Mills' syndrome or Kennedy's disease);
- less than two behavioural symptoms or only cognitive or only psychiatric symptoms.

**Assessment of studies**

A significant proportion of the included studies in part B was published before the diagnostic El Escorial criteria for ALS and the Neary criteria for a diagnosis of FTD were established.[14, 15] One of the authors (JR) assessed the diagnoses of these patients. This assessment was based on the clinical description in combination with the results of a pathological examination, which was available in 81 cases (48%). Based on descriptions of definite upper motor neuron signs and symptoms (forced yawning, crying and laughing, clonus of masseter reflex, (sub)clonic myotatic reflexes, Hoffmann-Trömner sign, extensor plantar response and spasticity) and, when available, results of a pathological examination, all patients could be classified as either PMA, ALS or PLS. Accordingly, based on clinical descriptions and pathological examination when available, patients could be labelled as FTD (including Pick's disease).

**Data extraction**

For part A: prevalence of bvFTD and mild behavioural changes in MND, the following data were extracted from the cohort studies: number of patients; percentage of ALS patients with bulbar onset; description of the patient sample; method used to assess bvFTD or mild behavioural changes; (point) prevalence of bvFTD or mild behavioural changes; description of the diagnosis, i.e. the definition of bvFTD.

For part B: bvFTD symptoms in MND patients, the following data were extracted from the case studies/case series: gender, age at onset, age at diagnosis, MND diagnosis (ALS, PMA or PLS), duration of disease, whether the patient was first diagnosed as MND or bvFTD, bulbar- or limb-onset MND, bvFTD symptoms (i.e. behavioural, cognitive and psychiatric symptoms).

**Data analysis**

Study, demographic and clinical characteristics were summarized with simple descriptive statistics.

- Part A: prevalence of bvFTD and mild behavioural changes in MND; point prevalence rates presented in the cohort studies were pooled, accounting for inter-study variation and analysed using a non-linear random effects model.
- Part B: bvFTD symptoms in MND patients; differences regarding gender, age, survival and site of onset (of ALS) between patients with ALS onset and patients with bvFTD onset were analysed using a two-group *t*-test or Mann-Whitney *U*-test, when appropriate. Data analyses were performed in SPPS version 17.0 and SAS 9.1 (module proc. nlmixed).
- Additional data analysis for part B: the descriptions of behavioural, cognitive and psychiatric disturbances, respectively, were categorized into bvFTD symptoms (see Table E-3). When memory problems were mentioned in the patient description, all of the following descriptions – 'disturbances', 'changes', 'impairment', and 'deficits' – were interpreted as 'memory disturbance', in the absence of a formal neuropsychological examination. A small number of studies reported neuropsychological test results; these were not analysed in this study. Percentages of the categorized bvFTD symptoms were calculated from patients in case studies or case series (numerator = number of patients with the disturbance; denominator = total number of patients). Using these percentages, pooled prevalence rates accounting for inter-study variation were analysed using a non-linear random effects model.







## RESULTS

### Part A: prevalence of bvFTD in MND patients

The search retrieved nine studies with prevalence rates of bvFTD in cohorts of MND patients (Table 1). ALS patients were studied in eight studies [10, 12, 16-21]; ALS and PMA patients in one study.[22]

**Table 1.** Prevalence of the behavioural variant FTD in MND: results from cohort studies

| Behavioural variant of frontotemporal dementia in MND | | | | | | |
|---|---|---|---|---|---|---|
| **Author (ref.)** | **(n) Patients** | **Bulbar %** | **Patient sample** | **Assessment** | **Prevalence** | **Description** |
| Ringholz (10) | 279 | 34 | consecutive patients, two hospitals (USA) | NPE, (family) interviews | 5% | Behavioural variant FTD |
| Murphy (16) | 23 | 27 | volunteer cohort, multidisciplinary clinic (USA) | NPE, NPI, MRI | 9% | Behavioural variant FTLD |
| Lillo (12) | 92 | 22 | respondents to postal survey sent to members of patient association (Australia) | Clinical questionnaire for bvFTD symptoms and CBI-R | 11% | (estimated to) fulfil criteria for behavioural variant FTD |

**Table 1.** Continued.

| Behavioural variant of frontotemporal dementia in MND | | | | | | |
|---|---|---|---|---|---|---|
| **Author (ref.)** | **(n) Patients** | **Bulbar %** | **Patient sample** | **Assessment** | **Prevalence** | **Description** |
| Phukan (17) | 160 | 34 | population based (Ireland) | Direct evaluation, semi-structured interviews | 11% | behavioural variant FTD |
| Gibbons (22) | 16 | 13 | consecutive patients in MND clinic (UK) | Informant based semi-structured interview | 13% | Behavioural symptoms in the range seen in FTD |
| Portet (18) | 23 | 100 | bulbar ALS patients in a neurology clinic (France) | NPE, clinical examination during hospital admission | 18% | Severe behavioural changes consistent with FTD |
| Woolley (19) | 31 | 34 | subset of group of patients visiting two ALS clinics (USA); validation cohort for a new screening instrument | NPE, FrSBe | 19% | FTD |
| Lepow (20) | 37 | n.g. | subset of patients visiting an ALS clinic who underwent further testing after screening (USA) | NPE, FrSBe | 19% | FTD |
| Lomen-Hoerth (21) | 44 | 43 | subset of patients: out of 100 consecutive patients of ALS clinic who either underwent further testing after screening, or were referred to a memory clinic (USA) | NPE, NPI, CDR | 27% | Research criteria for probable and definite behavioural variant FTLD |

*n* = number of patients; bulbar % percentage of ALS patients with bulbar-onset; n.g. not given; NPE neuropsychological examination; NPI Neuropsychiatric Inventory; CBI-R Cambridge Behavioural Inventory-Revised; FrSBe Frontal Systems Behavior Scale; CDR Clinical Dementia Rating Scale; FTD frontotemporal dementia; FTLD frontotemporal lobar degeneration.

**Table 2.** Prevalence of mild and moderate behavioural impairment in MND without dementia: results from cohort studies

| Mild and moderate behavioural impairment in MND | | | | | | |
|---|---|---|---|---|---|---|
| **Author (ref.)** | **(n) Patients** | **Bulbar %** | **Patient sample** | **Assessment** | **Prevalence** | **Description** |
| Murphy (16) | 23 | 27 | volunteer cohort, multidisciplinary clinic (USA) | NPE, NPI, MRI | 17% | Score of 3 or more (max = 12) on 2 or more behaviors (NPI) |
| Woolley (19) | 31 | 34 | subset of group of patients visiting two ALS clinics comprising a validation cohort for a new screening instrument (USA) | NPE, FrSBe | 19% | Mild behavioural impairment with or without mild cognitive impairment |
| Lillo (12) | 92 | 22 | respondents to postal survey sent to members of MND patient association (Australia) | Clinical questionnaire for bvFTD symptoms and CBI-R | 20% | Moderate behavioural change not fulfilling bvFTD |
| Witgert (23) | 225 | 24 | Consecutive sporadic ALS patients from ALS clinic (USA) | FrSBe | 24% | >1.5 SD on total FrSBe score |
| Woolley (24) | 16 | 6 | Recruited from ALS clinic (USA) | FrSBe | 25% | >1.5 SD on total FrSBe score |
| Chio (25) | 70 | 23 | Consecutive patients from ALS clinic (Italy) | FrSBe | 49% | >1.5 SD on total FrSBe score |
| Meier (26) | 18 | n.g. | Recruited from MND clinic (New Zealand) | NPI | 50% | Score of 3 or more (max = 12) on 2 or more behaviors (NPI) |
| Gibbons (22) | 16 | 13 | consecutive patients in MND clinic (UK) | Informant based semi-structured interview sensitive to bvFTD | 88% | Some sort of change in affect and/or social conduct |

*n* number of patients; bulbar % percentage of ALS patients with bulbar-onset; n.g. not given; NPE: neuropsychological examination; NPI Neuropsychiatric Inventory; CBI-R Cambridge Behavioural Inventory-Revised; FrSBe Frontal Systems Behaviour Scale; CDR Clinical Dementia Rating Scale; FTD frontotemporal dementia; FTLD frontotemporal lobar degeneration.

In four studies selection bias was evident from the patient sample description: only bulbar-onset MND patients were included[18]; or cohorts consisted of subsets of MND patients who underwent further neuropsychological investigation after an initial screening.[19-21] In the remaining five studies, which either included consecutive MND patients visiting a clinic, or members of a MND patient association responding to a postal survey, or a population based cohort, the prevalence of bvFTD according to Neary's criteria ranged from 5.3% to 12.5% (Table 1).[10, 12, 16, 17, 22] The pooled prevalence rate of bvFTD in MND taken from these five studies is 8.1% (*n*= 570; 95% CI 5.6 – 11.5%).

**Prevalence of mild behavioural changes in MND patients**

The search retrieved eight studies with prevalence rates of mild (*n* = 7) or moderate (*n* = 1) behavioural changes in cohorts of MND patients without dementia (Table 2).[12, 16, 19, 22-26]

ALS patients were studied in seven studies; ALS and PMA patients in one study.[22] Mild to moderate behavioural changes (according to diverging definitions) were shown in 17 – 88% of MND patients (Table 2). The search retrieved another six studies that examined mild behavioural changes in MND patients without presenting prevalence rates. These data are summarized in a supplementary table (Table E-1). Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/17482968.2012.656652.

**Part B: clinical characteristics of MND-bvFTD patients**

In this part of the review, data from individual patients from case studies or case series were analysed. From the literature search 20 reports were excluded that reported patients with MND variants, Alzheimer's disease, less than two behavioural symptoms, or only cognitive symptoms. Ninety-eight articles met the inclusion criteria for part B (Figure 1, and supplementary table E-2 for the articles included). Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/17482968.2012.656652.

In these 98 studies, 170 patients were described: 135 ALS patients, 21 PMA patients and three PLS patients; one patient had progressive bulbar palsy without central motor neuron signs and was included in the PMA group; no information on reflexes or pyramidal tract involvement was available from 10 other patients, and these were included in the ALS group. Of the 170 patients, 142 could also be classified as suffering from bvFTD or Pick's disease, and 28 as probable bvFTD. In the following sections the Pick's disease and probable bvFTD cases are included in the 'bvFTD' group. Clinical and demographic data are summarized in Table 3.





**Table 3.** Clinical and demographic data of 170 patients with MND-bvFTD

| | bvFTD onset | MND onset | Simultan. onset | Unknown onset | Total (N) ¶ |
|---|---|---|---|---|---|
| **Total** | 93 | 36 | 32 | 9 | 170 |
| Male | 49 | 21 | 21 | 4 | 95 |
| Female | 42 | 15 | 11 | 3 | 71 |
| Missing | 2 | 0 | 0 | 2 | 4 |
| **Age at onset, y** | 53 (16 – 73) **§** | 64 (25 – 80) | 53 (32 – 66) | 43 (38 – 70) | 54 (16 – 80) |
| Missing | 19 | 5 | 4 | 4 | 32 |
| **Survival* months** | 36 (9 – 156) **§** | 29 (12 – 108) | 23 (12 – 99) | 36 (15 – 84) | 33 (9 – 156) |
| Missing | 38 | 12 | 17 | 4 | 71 |
| **Onset MND** | | | | | |
| Limb | 34 | 16 | 16 | 4 | 70 |
| Bulbar | 41 | 16 | 13 | 1 | 71 |
| Limb and bulbar | 10 | 2 | 3 | 1 | 16 |
| Missing | 8 | 2 | 0 | 3 | 13 |

Values are totals, or median (range). Simultan.: simultaneous onset of ALS and bvFTD; Y: years. ¶: ALS (*n* 145); PMA (*n* 22); PLS (*n* 3); *: duration between the first symptom as reported by the patient or a relative, and death. **§**: *p* 0.01 compared to patients with MND onset.

The male to female ratio of the 170 MND-FTD patients was 1.3:1. BvFTD developed after a median time of 16 months in MND patients (range 2 – 40; *n* = 21, missing data 42%); MND developed after a median time of 18 months in bvFTD patients (range 2 – 168; *n* = 60; missing data 35%, difference not significant between MND or bvFTD onset). Forty-two percent of the MND-bvFTD patients had bulbar-onset MND and 41% had limb onset. Site of onset was not significantly different between patients with MND and bvFTD onset (missing data 3%). When ALS-bvFTD patients were analysed separately, the proportion of bulbar, limb, and simultaneous limb and bulbar onset was 48%, 39% and 10%, respectively (missing data 3%).

**BvFTD symptoms: characteristics, relative frequencies and pooled prevalences**

From the descriptions of 170 MND-bvFTD patients, 59 different bvFTD symptoms were listed in a supplementary table (Table E-3). Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/17482968.2012.656652.

The number of bvFTD symptoms reported per patient, and their frequencies, are shown in Table 4.

**Table 4.** Number of bvFTD symptoms reported per patient

| Number of bvFTD symptoms | Number of patients | Cumulative percentage |
|---|---|---|
| 2 | 23 | 13.5 |
| 3 | 28 | 30.0 |
| 4 | 23 | 43.5 |
| 5 | 27 | 59.4 |
| 6 | 16 | 68.8 |
| 7 | 12 | 75.9 |
| 8 | 12 | 82.9 |
| 9 | 10 | 88.8 |
| 10 | 8 | 93.5 |
| > 10 | 11 | 100.0 |
| Total | 170 | |

In total 960 bvFTD symptoms were described in 170 patients (mean 5.6 bvFTD symptoms per patient). Pooled prevalence rates showed that perseveration was the most frequently described behavioural disturbance (40%). Apathy and disinhibition showed pooled prevalence rates of 29 and 26%, respectively (Figure 2). Three cognitive symptoms were listed: memory disturbances, attention deficits and disorientation. Memory disturbances, ranging from mild to severe showed a pooled prevalence of 43%. Memory disturbance was the first bvFTD symptom in 20% of the patients. Of the psychiatric symptoms, delusions, paranoia and hallucinations showed a pooled prevalence rate of 9, 8 and 12%, respectively.

## DISCUSSION

This systematic review shows that 8% of MND patients have bvFTD and that perseveration, apathy and disinhibition are the most frequently described behavioural symptoms of patients with MND-bvFTD. We also found that bvFTD occurs relatively more often in bulbar-onset MND. A noticeable finding is the high frequency of memory disturbance in MND-bvFTD patients.

### Prevalence of FTD

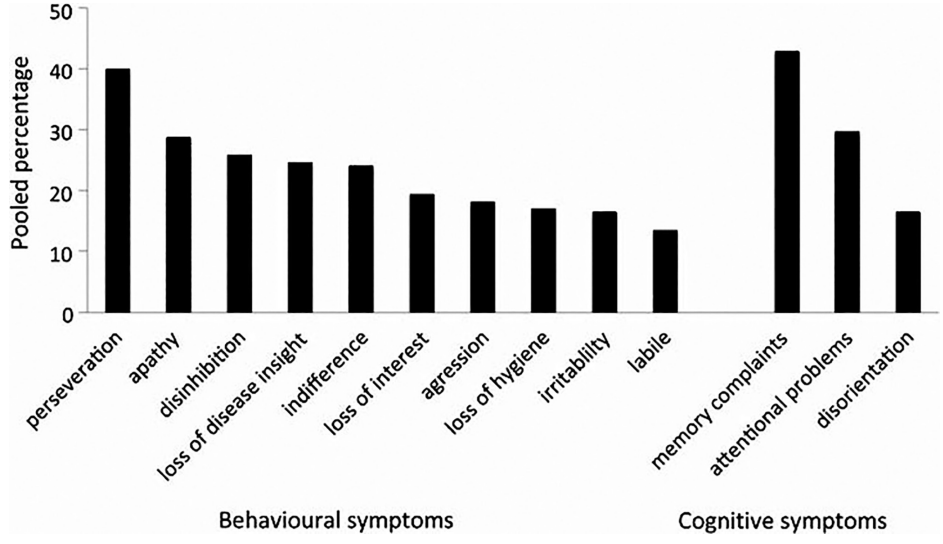
The prevalence of bvFTD in MND in this review varied between 5% and 27%, which is related to diverging definitions (i.e. research criteria for probable FTD vs. Neary criteria) and different patient samples (e.g. a subset of patients investigated after an initial screening test vs. population based samples). The study with the largest cohort, including 279 ALS patients shortly after diagnosis had been established, showed a lower prevalence of bvFTD (5%) compared to the population or 'patient-association based' studies (11%), which encompassed MND patients with a longer disease duration.[10, 12, 17] This higher prevalence of





bvFTD in the latter studies may reflect the development of bvFTD in the course of MND.

**Figure 2.** Most frequently described bvFTD symptoms in MND patients




Percentages denote the estimated prevalence of MNDbvFTD patients with the particular bvFTD symptom reported in case reports or series. Percentages presented in 98 studies were pooled using a non-linear random effect analysis. Here, the 10 most frequently reported behavioural symptoms and three cognitive symptoms are shown. Supplementary Table 3 shows a complete list of the estimated prevalences of bvFTD symptoms.

### Clinical variables – MND or bvFTD: which disease comes first?

There has been debate in the literature on whether the occurrence of bvFTD precedes that of MND in nearly all patients with MND-bvFTD[27], or whether bvFTD develops in the course of MND. Taking into consideration the differences in disease duration between FTD (6 – 8 years) and MND (three years), and presuming that the chance of developing one disease when the other is present, is equal, then FTD patients have at least twice as much time to develop MND, compared to MND patients to develop FTD.[28, 29]

In agreement with this assumption, in 161 MND-bvFTD patients in this systematic review 55% presented with bvFTD, 21% with ALS and in 19% there was a simultaneous onset. In comparison, a recent study in 31 behavioural predominant MND-FTD patients showed 68% patients presenting with bvFTD, 10% with MND and 22% with a simultaneous onset.[30] Differences in disease onsets in MND-bvFTD cohorts may be related to the site where patients are recruited (i.e. dementia clinic vs. MND clinic).

**Clinical variables: bulbar-onset ALS**

There have been conflicting data about a relationship between FTD and bulbar-onset MND/ALS.[10, 17, 21] Depending on whether a cohort with prevalent or incident MND/ALS patients (without dementia) is studied, 19 – 30% of MND/ALS patients have bulbar onset.[28, 31] In this systematic review we found bulbar onset in 42% of MND-bvFTD (48% of ALS-bvFTD patients), which is within the range found by two other studies (39 – 61%) in patients with MND-bvFTD.[29, 30] This supports an association of bulbar onset and extramotor cortex involvement in MND.

**Clinical variables: survival**

In this study, MND-bvFTD patients with MND onset had a shorter survival compared to MND-bvFTD patients with bvFTD onset (Table 3). Compared to the survival of bvFTD patients without MND, the development of MND in bvFTD patients reduces survival by at least 50%.[29] The survival of all MND-bvFTD patients in this review with complete data is 13 months shorter compared to findings of a retrospective study, which may be related to the higher proportion of MND-onset patients (22% vs. 10%) in our study.[30] When only bvFTD-onset MND-bvFTD patients were analysed, the survival in the present study (36 months) was similar, respectively seven months longer compared to two smaller studies in MND-bvFTD patients[29, 32]; the difference may be ascribed to a higher proportion of bulbar-onset ALS patients in one of the latter studies.[29] Thus, our review corroborates earlier findings that the occurrence of MND in bvFTD leads to a shorter survival. Interestingly, the survival of MND patients who developed bvFTD is similar to a population based prospective survey in MND patients with a comparable age at onset and a lower proportion bulbar-onset MND.[28] Thus, our data do not support the observations made by others that bvFTD leads to a shorter survival in MND[11, 13, 32], although missing data in 33% made this finding less reliable.

A negative effect of bvFTD on survival in MND has been shown by others to be related to a higher non-compliance with non-invasive ventilation and feeding tube insertion, and to a higher proportion of bulbar-onset MND in MND-bvFTD.[13] Therefore, the impact of FTD on the survival of MND patients, irrespective of these confounders, needs to be studied further.[11]

**Cognitive variable: memory disturbance**

This review shows that 43% of MND-bvFTD patients had early or severe memory disturbances, ranking memory as the most frequent bvFTD symptoms in MND-bvFTD. Although early or severe memory problems are traditionally considered to be rare in bvFTD, initial memory complaints have been reported in 16 – 60% of bvFTD patients, and in one study memory problems were the fourth most frequent of 12 bvFTD symptoms.[29, 33, 34] In 20% of the MND-bvFTD patients in





the present study, memory disturbance was among the first symptoms, which is in agreement with a recent study in 18 MND-FTD patients.[29] Of note, in our and other studies, memory disturbances were based on history taking, which may have overestimated the frequency, because other cognitive deficits may have been misinterpreted as memory disturbances.

**Mild behavioural symptoms in MND**

The presence of mild behavioural changes in MND would support the concept of a continuum between MND and bvFTD. In 13 of the 14 retrieved studies concerning mild behavioural changes, these were assessed with the Frontal Systems Behaviour Scale, Neuropsychiatric Inventory or Cambridge Behavioural Inventory. These instruments, widely used in patients with dementia, have not been validated in MND patients and are not adapted for motor impairment, which probably results in overestimation of 'motor-free' mild behavioural changes in MND. In addition, in only three studies a control group was examined.[35, 36] A prospective controlled study with a clear description of the inception cohort with a valid scale is needed to assess the presence of mild behavioural changes in MND. The behavioural characteristics of MND in this review may help to develop such a scale.

**Strengths and limitations**

In addition to its strengths (large number of patients, systematic analysis) this review has some limitations. The methodological quality of case reports and case series is poor. We found, however, that most patient descriptions were sufficient to extract useful information, which is underlined by the description of at least four bvFTD symptoms in nearly three-quarters of the patients (Table 3).

The pooled prevalences of the bvFTD symptoms from the random effect analysis should be interpreted with caution. In single case studies or case series, authors may tend to describe symptoms that are prominent, interesting and in line with the diagnosis.

In conclusion, bvFTD is present in 8% of MND patients and perseveration, apathy and disinhibition are frequently described in MND-bvFTD. Memory disturbances are another important symptom for the clinician who evaluates a patient with MND, as it may be heralding the onset of bvFTD.

## ACKNOWLEDGEMENTS

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## SUPPLEMENTAL MATERIAL

Fourteen studies were found which examined mild behavioural changes in MND patients. The Frontal Systems Behaviour Scale (FrSBe) was used in 10 studies (table).[1-9] The Neuropsychiatric Inventory, Cambridge Behavioural Inventory-Revised, a clinical questionnaire or semi-structured interview were used in four other studies which are not discussed here.[10-13] The FrSBe is a behavioural scale with three subscales (apathy, disinhibition and executive dysfunction). Half of the 14 items measuring apathy are directly related to motor disabilities (limb or bulbar palsy) and the two other subscales (disinhibition and executive dysfunction) also contain some items related to motor disabilities. In all studies the apathy subscale showed higher scores compared to the other subscales (see table). In two of the three controlled studies a significantly higher score for apathy was shown compared to the control group.

**Table 1.**

| | | | | | FrSBe subscales (T-scores) | | |
|---|---|---|---|---|---|---|---|
| **Author (ref)** | **(n) Patients** | **Bulbar %** | **Control group** | **FrSBe total score (T-score)** | **Apathy** | **Disinhibition** | **Dys-executive** |
| Woolley[1] | 17 | n.g.* | no | 56 | 59 | 52 | 55 |
| Wicks[2] | 41 | 12 | | 55 | 58** | 54 | 54 |
| | | | *n = 35* | *50* | *50* | *49* | *48* |
| Woolley[3] | 16 | 6 | no | 57 | 60 | 55 | 56 |
| Chiò[4] | 70 | 23 | no | n.g. | 67 | 57 | 63 |
| Witgert[5] | 225 | 24 | no | 55 | 59 | 52 | 53 |
| Terada[6] | 24 | n.g. | no | 54 | 62 | 49 | 50 |
| Tsujimoto[7] | 21 | 33 | no | n.g. | 54 | 46 | 46 |
| Grossman[8] | 45 | 38 | no | | 56 | 29 | 47 |
| Girardi – 1^[9] | 17 | n.g. | | 56 | 57** | 55 | 55 |
| | | | *n = 20* | *51* | *46* | *53* | *47* |
| Girardi – 2^[9] | 14 | 7^^ | | 67 | n.g. | n.g. | n.g. |
| | | | *n = 20* | *75* | *n.g.* | *n.g.* | *n.g.* |

From all studies 'Post-Illness' scores rated by a carer were taken, except where stated otherwise. n.g.: not given; *: mean bulbar score ALSFRS-R 9; **: p<0.05; ^: self-rated scores were presented (no difference was found between carer-rated and self-rated scores); ^^: bulbar symptoms.

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**Table 2.** Reports of individual patients included in the review (adapted from original publication)

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Androp, S. | Amyotrophic lateral sclerosis with psychosis | Psychiatr Q,1940 |
| Anneser, J. | Inappropriate sexual behaviour in a case of ALS and FTD | Amyotroph Lateral Scler, 2007 |
| Bak, T. | Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 | Brain, 2001 |
| Benajiba, L. | TARDBP mutations in motoneuron disease with frontotemporal lobar degeneration | Ann Neurol, 2009 |
| Bonaretti, T. | Su due casi di sclerosi laterale amiotrofi ca ad inizio pseudobulbare preceduta da decadimento psichico | G Psichiatr Neuropatol, 1959 |
| Boudouresques, J. | État démentiel, sclérose latérale amyotrophique, syndrome extrapyramidal | Rev Neurol, 1967 |
| Boxer, A. | Clinical, neuroimaging and neuropathological features of a new chromosome 9p-linked FTD-ALS family | J Neurol Neurosur Ps, 2011 |
| Brandmeir, N. | Severe subcortical TDP-43 pathology in sporadic frontotemporal lobar degeneration with motor neuron disease | Acta Neuropathol, 2008 |
| Braunmühl, Von A. | Picksche Krankheit und amyotrophische lateral sklerose | Allgemeine Psychiatrisch Psychol Med, 1932 |
| Brion, S. | L'association maladie de Pick et sclérose latérale amyotrophique | L'Encéphale, 1980 |
| Broustal, O. | FUS mutations in frontotemporal lobar degeneration with amyotrophic lateral sclerosis | J. Alzheimers Dis, 2010 |
| Burnstein, M. | Familial amyotrophic lateral sclerosis, dementia, and psychosis | Psychosomatics, 1981 |
| Campanella, G. | Su di un caso di sclerosi laterale amiotrofi ca a caraterre familiare | G Psichiatr Neuropatol, 1959 |
| Cavalleri, F. | Amyotrophic lateral sclerosis with dementia | Acta Neurologica Scandinavica, 1994 |
| Chio, A. | Amyotrophic lateral sclerosis-frontotemporal lobar dementia in 3 families with p.Ala3882Thr TARDBP mutations | Arch Neurol, 2010 |

**Table 2.** Continued.

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Constantinidis, J. | Syndrome familial: association de maladie de Pick et scléroselatérale amyotrophique | L'Encéphale, 1987 |
| Dazzi, P. | Sulla sclerosi laterale amiotrofi ca familiare contributo clinico | G Psichiar Neuropatol, 1969 |
| De Brito-Marques, P. | Amyotrophic lateral sclerosis with dementia | Arq Neuropsiquiatr, 1999 |
| De Morsier, G. | Un cas de maladie de Pick avec sclérose latérale amyotrophiqueterminale | Rev Neurol, 1967 |
| Deng, H. | Mutations in UBQLN2 cause dominant X-linked juvenile and adult-onset ALS and ALS-dementia | Nature, 2011 |
| Deymeer, F. | Thalamic dementia and motor neuron disease | Neurology, 1989 |
| Dickson, D. | Klüver-Bucy syndrome and amyotrophic lateral sclerosis | Neurology, 1986 |
| Duffy, J. | Progressive apraxia of speech as a sign of motor neuron disease | Am J Speech Lang Pathol, 2007 |
| Dwornik, A. | Frontotemporal dementia with lower motor neuron disease and extrapyramidal signs: case description | J Neurol, 2007 |
| Enns, M. | Amyotrophic lateral sclerosis presenting with psychosis | Psychosomatics, 1993 |
| Finlayson, M. | Cerebral lesions in familial amyotrophic lateral sclerosis and dementia | Acta Neuropathol, 1973 |
| Friedlander, J. | Role of psychosis in amyotrophic lateral sclerosis | Arch Neurol Psychiatr, 1948 |
| Gentileschi, V. | Fronto-temporal dementia and motor neuron disease | Acta Neurol Scand, 1999 |
| Gibbons, Z. | Behaviour in amyotrophic lateral sclerosis | Amyotroph Lateral Scler, 2008 |
| Girardi, A. | Deficits in emotional and social cognition in amyotrophic lateralsclerosis | Neuropsychology, 2011 |
| Gunnarsson, L. | Motor neuron disease and dementia reported among 13 membersof a single family | Acta Neurol Scand, 1991 |
| Horopian, D. | Dementia and motor neuron disease: morphometric, biochemical, and golgi study | Ann Neurol, 1984 |





**Table 2.** Continued.

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Ichikawa, H. | Writing errors and anosognosia in amyotrophic lateral sclerosiswith dementia | Behav Neurol, 2008 |
| Ishihara, K. | An autopsy case of frontotemporal dementia with severe dysarthria and motor neuron disease | Neuropathology, 2006 |
| Josephs, K. | Clinically undetected motor neuron disease in pathologically proven frontotemporal lobar degeneration | Arch Neurol, 2006 |
| Kato, S. | Participation of the limbic system and its associated areas in the dementia of amyotrophic lateral sclerosis | J Neurol Sci, 1994 |
| Katz, J. | An I113T mutation in the SOD-1 gene associated with severe frontotemporal dementia in a patient with familial ALS | Amyotroph Lateral Scler, 2008 (abstract) |
| Kellner, M. | Letter to the Editor: Familial presenile dementia with motorneuron disease | J Clin Psychiatry, 1994 |
| Kim, S. | Semantic dementia combined with motor neuron disease | J Clin Neurosci, 2009 |
| Komachi, H. | Motor neuron disease with dementia and ophthalmoplegia | J Neurol, 1994 |
| Kurachi, M. | Amyotrophic lateral sclerosis with temporal lobe atrophy | Folia Psychiatr Neurol Jpn, 1979 |
| Kuwahara, H. | Frontotemporal lobar degeneration with motor neuron disease showing severe and circumscribed atrophy | J Neurol Sci, 2010 |
| Larner, A. | Delusion of pregnancy in frontotemporal lobar degeneration with motor neurone disease | Behav Neurol, 2008 |
| Léchelle, P. | Maladie de Pick. Sclérose latérale amyotrophique terminale | Ann Méd Interne, 1954 |
| Lillo, P. | Neurobehavioral features in frontotemporal dementia with amyotrophic lateral sclerosis | Arch Neurol, 2010 |
| Litterio, D. | Sclerosi laterale amiotrofi ca e demenza: una rara associazione. | Riv Neurol, 1985 |
| Liu, A. | A case study of an emerging visual artist with frontotemporal lobar degeneration | Neurocase, 2009 |

**Table 2.** Continued.

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Lopate, G. | Familial ALS with extreme phenotypic variability due to the I113T SOD1 mutation | Amyotroph Lateral Scler, 2010 |
| Lopez, O. | Dementia accompanying motor neuron disease | Dementia, 1994 |
| Luty, A. | Pedigree with frontotemporal lobar degeneration - motor neurondisease and Tar DNA binding protein-43 positive neuropathology | Neurology, 2008 |
| Marquard, R. | Dementia accompanying motor neuron disease | Dement Geriatr Cogn Disord, 2003 |
| Martinaud, O. | Frontotemporal dementia, motor neuron disease and tauopathy | Acta Neuropathol, 2005 |
| McCluskey, L. | Amyotrophic lateral sclerosis-plus syndrome with TAR DNAbinding protein-43 pathology | Arch Neurol, 2009 |
| Meyer, A. | Über eine der amyotrophischen Lateralsklerose nahestehende Erkrankung mit psychischen Störungen | Ztschr ges Neurol u Psychiat, 1929 |
| Mitsuyama, Y. | Progressive dementia with motor neuron disease | Eur Arch Psychiatry Neurol Sci, 1985 |
| Mitsuyama, Y. | Presenile dementia with motor neuron disease in Japan | Arch Neurol, 1979 |
| Mitsuyama, Y. | Presenile dementia with motor neuron disease: an additional casereport | Folia Psychiatr Neurol Jpn, 1981 |
| Mitsuyama, Y. | Presenile dementia with motor neuron disease in Japan: clinicopathological review of 26 cases | J Neurol Neurosurg Ps, 1984 |
| Mochizuki, A. | Frontotemporal dementia with ubiquitinated neuronal inclusions presenting with primary lateral sclerosis and parkinsonism | Acta Neuropathol, 2004 |
| Momeni, P. | Analysis of IFT74 as a candidate gene for chromosome 9p-linkedALS-FTD | BMC Neurol, 2006 |
| Moretti, R. | Complex cognitive disruption in frontal dementia related tomotor neuron disease | Percept Mot Skills, 2001 |





**Table 2.** Continued.

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Morita, K. | Presenile dementia combined with amyotrophy: a review of 34 Japanese cases | Arch Gerontol Geriatr, 1987 |
| Muller, M. | Amyotrophic lateral sclerosis and frontal lobe dementia inalzheimer´s disease | Eur Neurol, 1993 |
| Neary, D. | Frontal lobe dementia and motor neuron disease | J Neurol Neurosurg Ps, 1990 |
| Niizato, K. | Pick's disease with amyotrophic lateral sclerosis (ALS) | J Neurol Sci, 1997 |
| Nitrini, R. | Psychotic symptoms in dementia associated with motor neurondisease | J Neuropsychiatry Clin Neurosci, 1998 |
| Ojeda, V. | Familial motor neuron disease associated with non-specificorganic dementia | Med J Aust, 1984 |
| Olojugba, C. | De Clerambault's syndrome (erotomania) as a presenting feature of frontotemporal dementia and motor neuron disease | Behav Neurol, 2007 |
| Omar, R. | Delusions in frontotemporal lobar degeneration | J Neurol, 2009 |
| Pearson, J. | Familial frontotemporal dementia with amyotrophic lateral sclerosis and a shared haplotype on chromosome 9p | J Neurol, 2011 |
| Peavy, G. | Neuropsychological aspects of dementia of motor neuron disease | Neurology, 1992 |
| Poppe, Von W. | Klinisch- und pathologisch-anatomische Untersuchungen über Kombinationsformen praeseniler Hirnatrophien | Psychiat Neurol, 1963 |
| Portera-Cailliau, C. | A familial form of pallidoluysionigral degeneration and amyotrophic lateral sclerosis with divergent clinical presentations | J Neuropathol Exp Neurol, 2007 |
| Prudlo, J. | Chromosomal translocation t(18;21)(q23;q22.1) indicates novelsusceptibility loci for frontotemporal dementia with ALS | Ann Neurol, 2004 |
| Raaphorst, J. | Amyotrophische laterale sclerose en frontotemporale dementie | Ned Tijdschr Geneeskd, 2010 |

**Table 2.** Continued.

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Rakowicz, W. | Dementia and aphasia in motor neuron disease | J Neurol Neurosurg Ps, 1998 |
| Reda, G. | Su una particolare forma morbosa del presenium di difficile classifi cazione nosografica | Riv Neurol, 1953 |
| Robertson, E. | Progressive bulbar paralysis showing heredofamilial incidence and intellectual | Arch Neurol Psychiatr, 1953 |
| Rusina, R. | FTLD-TDP with motor neuron disease, visuospatial impairment and a progressive supranuclear palsy-like syndrome | Neurology, 2011 |
| Šarac, H. | Magnetic Resonance Imaging and Magnetic Resonance spectroscopy in a patient with amyotrophic lateral sclerosis | Coll Antropol, 2008 |
| Sathasivam, S. | Frontotemporal lobar degeneration with motor neurone disease | Int J Psychiatry Clin Pract, 2008 |
| Shirabe, T. | An autopsy case of amyotrophic lateral sclerosis with dementia | Kyushu N-Psych, 1970 |
| Souza de, L | Démence sémantique assosciée à une sclérose latérale amyotrophique | Rev Neurol, 2009 |
| Sudo, S. | Motor neuron disease with dementia combined with degeneration of striatonigral and palliduluysian systems | Acta Neuropathol, 2002 |
| Takeda, T | Letter to the editor: Preferential involvement of the basolaterallimbic circuit in an amyotrophic lateral sclerosis patient | Eur J Neurol, 2007 |
| Tanaka, M. | Cerebral blood flow and oxygen metabolism in progressive dementia associated with amyotrophic lateral sclerosis | Neurol Res, 2003 |
| Thiel, A. | Demenz und psychotische Symptome bei der amyotrophenLateralsklerose | Nervenarzt, 1993 |
| Toyoshima, Y. | Is motor neuron disease-inclusion dementia a forme fruste of alswith dementia? | Neuropathology, 2005 |





**Table 2.** Continued.

| Author | Title (truncated) | Journal, year of publication |
|---|---|---|
| Tsuchiya, K. | Constant involvement of the Betz cells and pyramidal tract inamyotrophic lateral sclerosis with dementia | Acta Neuropathol, 2002 |
| Tsuchiya, K. | Atypical amyotrophic lateral sclerosis with dementia mimicking frontal Pick's disease | Acta Neuropathol, 2001 |
| van Es, M. | A case of ALS-FTD in a large FALS pedigree with a K17I ANGmutation | Neurology, 2009 |
| Van Reeth, P. | Démence de Pick assosciée à une sclérose latérale amyotrophique atypique | Acta Neurol Psychiatrica Belgica, 1961 |
| Vance, C. | Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2-21.3 | Brain, 2006 |
| Vercelletto, M. | Aspects neuropsychologiques et scintigraphiques des démencesfronto-temporales précédant l'atteinte du motoneurone | Rev Neurol, 2003 |
| Vercelletto, M. | Démence de type frontal et sclérose latérale amyotrophique | Rev Neurol, 1995 |
| Wilhelmsen, K. | 17q-linked frontotemporal dementia-amyotrophic lateral sclerosis without tau mutations with tau and alpha-synuclein inclusions | Arch Neurol, 2004 |
| Yokota, O. | Amyotrophic lateral sclerosis with dementia | Acta Neuropathol, 2006 |
| Yvonneau, M. | Syndrome familial de sclérose latérale amyotrophique avecdémence | L'Encéphale, 1971 |

From patients in case studies or case series, percentages of the categorized bvFTD symptoms were calculated (numerator = number of patients with the disturbance; denominator = total number of patients). Using these percentages, pooled prevalence rates accounting for inter-study variation were analysed using a nonlinear random effects model. These pooled prevalence rates are listed in this table.

**Table 3.**

| bvFTD symptom | Prevalence rate | bvFTD symptom | Prevalence rate |
|---|---|---|---|
| memory complaints | 42.9 | anxious | 5.3 |
| perseveration | 40.0 | loss of initiative | 4.7 |
| attention deficit | 29.8 | wasting money | 4.7 |
| apathy | 28.8 | poverty of speech | 4.7 |
| disinhibition | 25.9 | loss of emotions | 4.7 |
| loss of disease insight | 24.7 | obsession with food | 4.1 |
| indifference | 24.1 | spontaneous | 4.1 |
| loss of interest | 19.4 | loss of will | 4.1 |
| aggression | 18.2 | suspicious | 3.6 |
| loss of hygiene | 17.1 | selfishness | 3.5 |
| disorientation | 16.5 | imitation | 3.5 |
| irritability | 16.5 | alcohol addiction | 2.9 |
| labile | 13.5 | going away | 2.9 |
| mental rigidity | 12.9 | stubborn | 2.9 |
| restlessness | 12.9 | uncritically | 2.4 |
| hallucinations | 11.8 | insomnia | 2.4 |
| withdrawal behaviour | 11.2 | counteracting | 2.4 |
| wandering | 10.6 | desperate | 2.4 |
| hoarding | 10.6 | antisocial | 1.8 |
| loss of judgement | 10.6 | obsession with money | 1.8 |
| loss of decorum | 10.0 | inactive | 1.8 |
| impulsive | 10.0 | superficial | 1.8 |
| loss of empathy | 9.4 | loss of emotions | 1.2 |
| delusion | 9.4 | kleptomania | 1.2 |
| childish | 8.8 | narcissism | 1.2 |
| euphoria | 8.2 | attentiveness | 1.2 |
| paranoia | 7.6 | sad | 1.2 |
| obsessive | 7.1 | changes of activity level | 0.6 |
| sexually disinhibited | 7.1 | extravagance | 0.6 |
| excessive social behaviour | 6.5 | | |

# PART 2

## Screening for cognitive and behavioural impairment

# 5

## The verbal fluency index: Dutch normative data for cognitive testing in ALS

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## ABSTRACT

**Objective**
Executive dysfunction occurs in 30-50% of amyotrophic lateral sclerosis (ALS) patients and is most frequently assessed with the verbal fluency test. The verbal fluency index (VFI) has been developed to correct for slowness of speech in ALS, and reflects the average thinking time per word. However, its use as a marker of cognitive impairment is hindered by the absence of valid norm scores. Therefore, we provide normative data for the VFI.

**Methods**
Dutch volunteers were demographically matched to the Dutch ALS population and completed the verbal fluency index (one-minute and three-minute spoken letter fluency). Multiple stepwise linear regression was performed to assess the influence of demographic variables, past medical history and medication use.

**Results**
273 volunteers participated in this study. Educational level was negatively correlated to one-minute and three-minute VFI performance (r=-0.3 and r=-0.4, p<0.001, respectively). No correlations for age, gender, medication and past medical history were found. A formula for standardized z-scores, corrected for educational level, for the one-minute and three-minute VFI was calculated.

**Conclusions**
We provide Dutch normative data for the spoken verbal fluency index, which can be used internationally, but validation in other languages is recommended. The findings illustrate the importance of valid disease-specific norm scores for time-dependent cognitive tests in ALS.






## INTRODUCTION

In 30-50% of amyotrophic lateral sclerosis (ALS) patients cognitive changes have been demonstrated, in particular executive dysfunction.[1] Verbal fluency is a sensitive and reliable test of executive functioning and is used as a marker of cognitive performance in ALS.[2-5] Verbal fluency performance is related to educational level and age.[6] Because verbal fluency is a time-dependent task, it is important to correct for slowing of speech in ALS patients. For this reason, the verbal fluency index (VFI) has been developed, which represents the average thinking time per word.[7] Most frequently, one-minute and three-minute versions of the spoken version of the VFI (letter fluency) are used.[8-10] Preliminary English normative VFI data did not include correction for educational level or age and were based on 20 healthy controls who had a slightly higher educational level than the ALS patients, possibly overestimating dysfunction in patients.[8] The interpretation of fluency deficits in ALS patients can be further improved with normative VFI data based on a larger sample of controls. This cohort should be carefully matched with ALS patients on demographic variables that may exert an effect on letter fluency performance, i.e. education and age.[11] Our aim was to provide normative data for the one- and three-minute letter fluency index.



## METHODS

**Study population**
Two hundred and ninety-five native Dutch speaking volunteers participated in a population-based epidemiological ALS-study in the Netherlands (PAN) and were selected by general practitioners who look after patients with ALS.[12] The volunteers were matched for age, gender and education to 1009 ALS patients of the PAN study, included between June 2006 and May 2012. No VFI data of ALS patients are presented in this study; the demographic data of the ALS patients were only used to analyse whether the cohort matched with a representative ALS population. This study was approved by the Ethics Committee of the University Medical Centre Utrecht, and procedures were according to the Helsinki Declaration of 1975, revised in 1983.

**Demographic variables**
The past medical history and use of alcohol and sedative medication were recorded and dichotomized with 0 indicating no supposed effect on VFI performance and 1 indicating a possible effect on VFI performance (e.g. epilepsy in past medical history, use of sedative medication or three or more alcohol units per day).[13] The level of education was classified into seven categories,

ranging from primary school to university degree, which closely resembles the International Standard Classification of Education (ISCED, 2011).[14]

**Procedures**

Research assistants of the Dutch epidemiological study were trained twice by two authors (EB and JR) and administered the VFI to the volunteers during a home visit.[12] Participants were asked to name as many words beginning with the letter "D" in three minutes. The letter "D" was chosen following a strategy comparable to that used for the COWAT fluency test by Benton and Hamsher. This strategy is based on the frequency of words starting with a certain letter in a language.[15] The letter "D" in Dutch resembles the letters "F" and "S" in English, in terms of difficulty.[16] Names, variations of the same word (e.g. "door" followed by "doors"), same words with a different suffix (e.g. "doorknob" followed by "doorpost"), repetitions and non-existing words were not permitted. The number of words after one and three minutes was recorded. The VFI (letter version) consists of two conditions: in the generation condition participants name as many words beginning with a certain letter in three minutes. In the control condition, participants have to read aloud these produced items as quickly as possible. The fluency index is calculated as follows:

VFI = (time needed for generation - time needed for reading)/total number of items generated.[7]

The VFI reflects the average thinking time needed to generate a word. We used the spoken version of the VFI in this study. To screen for executive dysfunction, the frontal assessment battery (FAB) was administered to all participants (maximum score is 18; scores <14 indicate frontal/executive dysfunction).[17]

**Statistical analysis**

The volunteers were matched to 1009 ALS patients for age (independent t-test), gender (chi-square test) and level of education (Mann-Whitney U test). To examine the effects of age, gender, education, medication, past medical history and alcohol use on VFI scores in the volunteer group, multiple stepwise linear regression was used. Mean (SD) or median (interquartile range) was calculated, when appropriate, for the number of words generated after 1 and 3 minutes and the one-minute and three-minute VFI.





## RESULTS

**Study population**

Twenty-two participants with more than 5 errors (mainly rule-breaks) were excluded. Data of 273 participants were analysed (165 males, 60.4%). The mean (SD) age was 64.0 years (9.2, range 29-84). The median (interquartile range) educational level was 4 (3-6) and ranged from 'primary school' (n= 13) to 'university degree' (n= 18, table 1). The median (interquartile range) FAB score was 17 (16-18), indicating no frontal/executive dysfunction.

**Table 1.** Levels of education of the volunteers

| Level of education | | Number of volunteers (%) |
|---|---|---|
| 1 | Primary school | 13 (4.8) |
| 2 | Lower secondary education | 49 (17.9) |
| 3 | Upper secondary education | 67 (24.5) |
| 4 | Post-secondary education | 46 (16.8) |
| 5 | First stage of tertiary education | 28 (10.3) |
| 6 | College degree | 52 (19.0) |
| 7 | University degree | 18 (6.6) |

Levels of education are categorized according to the International Standard Classification of Education 2011, excluding the levels 0 (less than primary), 8 (doctoral) and 9 (not elsewhere classified).

The volunteers were matched for age (p = 0.1) and gender (p = 0.8) to the ALS patients in the PAN study: mean age 63.0 (10.9); 603 males (59.8%), 406 females. The distribution of education levels of the volunteer cohort and the PAN study cohort was comparable (p= 0.08).

**Verbal fluency index**

The mean (SD) number of words (raw score) of the one-minute and three-minute versions was 11.0 (3.9) and 22.8 (7.6), respectively. The median (interquartile range) VFI of the one-minute and three-minute versions was 4.7 (3.5-6.4) and 7.0 (5.6-9.5), respectively. Educational level was negatively correlated to one-minute and three minutes VFI performances (r=-0.3 and r=-0.4; p<0.001, respectively). There was no effect of age, gender, medication, past medical history and use of alcohol on VFI scores. The regression formula for the transformation of raw scores into a standardized z-score for the VFI one-minute version was z = (7.39 – (0.50 * education) – VFI)/2.72; and for the three-minute version this was z = (11.23 – (0.81 * education) – VFI)/3.46. For "education" we used the classification ranging from 1 to 7, as shown in table 1.

## DISCUSSION

In this study we provide normative data for a spoken fluency test for Dutch ALS patients based on a large dataset. Verbal fluency index (VFI) scores in the present study correlated to the level of education, with better performance in higher educated subjects, which is similar to conventional fluency tests, that are not corrected for motor slowness. Fluency performance on conventional tests increases until 30-39 years of age with only a mild decline after the age of 70.[6] We did not find age-related differences on VFI performance in our volunteer cohort. The majority of the volunteers were between 40 and 70 years of age, which might explain the absence of an age effect in this cohort.

Data collection for the *written* version of the VFI is in progress and a preliminary analysis of 34 participants showed an effect of education on VFI, comparable to the spoken version (data not shown).

A possible drawback of our study is that the test was administered in the home setting, where subjects may be easily distracted (e.g. by telephone). However, this setting could also be an advantage, as cognitive testing in ALS patients is frequently performed at home to spare them the fatigue of travelling.[1]

Twenty-two participants were excluded due to a high number of errors on the VFI. The errors consisted mainly of rule-breaks, i.e. 'door' followed by 'doors'. These participants did not show evidence of frontal lobe dysfunction on the FAB and did not differ from the included participants on demographic variables. Therefore, we assume that for these participants the instructions of the VFI have not been sufficiently clear. An exploratory regression analysis including these 22 participants did not change the regression coefficients.

Currently available English norm scores of the VFI for ALS patients are not corrected for education or age. They are based on a cut-off of 2 standard deviations below the mean of the scores of 20 healthy controls, who had a relatively high level of education, compared to the ALS patients.[8] Importantly, the present study is based on 273 subjects with a wide range of age and educational levels, comparable to a Dutch ALS population. Therefore, our normative data and z-score transformation formula can be used to further improve the assessment of letter fluency deficits in ALS patients.[3, 5] According to the consensus criteria for cognitive impairment in ALS, a score below the 5$^{th}$ percentile is considered abnormal, which corresponds to a z-score below -1.64.[18]





These normative data might be used internationally as the letter "D" in Dutch was chosen following a strategy similar to that used for the COWAT test and the classification of educational levels is comparable to the ISCED 2011.[11, 14] We recommend validation of our findings in other countries.

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# 6

## Screening for cognition in amyotrophic lateral sclerosis: test characteristics of a new screen

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## ABSTRACT

Cognitive and behavioural impairment in amyotrophic lateral sclerosis (ALS) negatively influence quality of life and survival, and therefore screening for these impairments is recommended. We developed a cognitive screening tool, the amyotrophic lateral sclerosis – frontotemporal dementia – cognitive screen (ALS-FTD-Cog) and aimed to validate it in patients with ALS. During the current study the Edinburgh cognitive and behavioural ALS screen (ECAS) was published and we therefore decided to compare these two cognitive screening methods.

The ALS-FTD-Cog was administered to 72 patients with ALS, 21 patients with behavioural variant FTD (bvFTD) and 34 healthy controls. Twenty-nine patients with ALS underwent the ECAS. ROC curve analyses were performed and sensitivity and specificity of the ALS-FTD-Cog and ECAS were calculated, with a neuropsychological examination (NPE) as gold standard.

Cognitive impairment was present in 28% of patients with ALS. ROC curve analyses of the ALS-FTD-Cog and ECAS showed an area under the curve (AUC) of 0.72 (95% CI 0.58-0.86) and 0.95 (95% CI 0.86-1.03), respectively. Compared to a full NPE sensitivity and specificity of the ALS-FTD-Cog were 65.0% and 63.5% and of the ECAS 83.3% and 91.3%, respectively. The sensitivity and specificity of the ALS-FTD-Cog in patients with bvFTD were 94.4% and 100%, respectively.

Test characteristics of the ALS-FTD-Cog were moderate, suggesting restricted practical value, as compared to a comprehensive NPE. The ECAS had an excellent AUC and high sensitivity and specificity, indicating that it is a valid screening instrument for cognitive impairment in ALS.






## INTRODUCTION

Cognitive impairment is present in 30-50% of patients with amyotrophic lateral sclerosis (ALS) and negatively influences survival and quality of life.[1-4] Investigation of cognition, in addition to behaviour, is therefore recommended in patients diagnosed with ALS.[5, 6]

The gold standard for measuring cognitive impairment is a full neuropsychological examination (NPE), which should be adapted to avoid bias due to impaired dexterity and speech.[5] An NPE is often a time consuming procedure, which might be a burden for the patient and not readably available in every neuromuscular clinic. Therefore, a concise screening tool could be useful. Currently, there are multiple cognitive screening tools available, but at the start of our study, only the ALS cognitive behavioral screen (ALS-CBS) and the Penn State Screening examination of Frontal and Temporal dysfunction Syndromes (PSSFTS) were published.[7-11] These screens are concise, with an administration time of 5 to 10 minutes.[12] However, not all cognitive domains known to be affected in ALS are included in these screens, i.e. tests of social cognition are lacking.[13]

The aim of the current study was to investigate the clinical validity of a new cognitive screening tool, the ALS - frontotemporal dementia - cognitive screen (ALS-FTD-Cog), which aims to cover the complete cognitive profile of ALS.[13] It consists of four frequently used cognitive tests. We hypothesized that the sensitivity of the screen would be high, as these tests have previously been demonstrated to show impairment in ALS patients. Furthermore, we expected the screen to be feasible in patients with ALS and widely applicable as the individual tests of the screen are not hampered by physical or speech impairment and normative data are available.[13-16]

During our study, the Edinburgh cognitive and behavioural ALS screen (ECAS) was published, which has become a widely used screening tool for cognitive impairment in ALS.[9] We therefore compared test characteristics of the ALS-FTD-Cog and ECAS in a subset of our study sample.

## METHODS

### Participants

Patients with ALS were recruited from our tertiary referral centres (Amsterdam University Medical Centers and University Medical Center Utrecht) in the Netherlands. All patients (sporadic or familial) had a diagnosis of probable

or definite ALS[17], a symptom duration of less than 12 months and an upright forced vital capacity of >70%, as described previously.[18] We also included a positive control group of (sporadic or familial) patients with behavioural variant FTD (bvFTD)[19] with or without ALS from our tertiary referral centre (Alzheimer Centre, Amsterdam University Medical Centers). A negative control group consisted of healthy controls without a history of neurological or psychiatric disease, who were approached through social media. All participants had to be older than 18 years, had to have a reliable informant and had to be fluent in Dutch.

The local medical ethical committees of the participating hospitals approved the study. Written informed consent was obtained from all participants. This study was performed in agreement with the Declaration of Helsinki.

**Procedures**

***The ALS-FTD-Cog***

The ALS-FTD-Cog is a screening tool which consists of the Faux pas test (FPT, social cognition), Rivermead behavioural memory test – story recall (RBMT, verbal memory), letter fluency index (LFI, executive function) and the Boston naming test (BNT, language).[13] All tests have validated norm scores, adjusted for age and education. The RBMT, LFI and BNT have previously shown to be impaired in ALS patients.[14-16] Social cognition deficits have more recently been recognized in ALS.[20, 21] A recent meta-analysis showed comparable effect sizes for tests of theory of mind and facial emotion recognition, suggesting that both concepts of social cognition are impaired in patients with ALS.[22] The ALS-FTD-Cog was administered during a home visit by a trained member of the research team, in a quiet room without distractions.

***Neuropsychological examination***

A full neuropsychological examination was performed in the outpatient clinic in all participants, as described previously, within 4 weeks from the administration of the screen.[18] Cognitive tests were chosen that were not hampered by motor or speech disabilities, or adaptations were made (see supplemental material). Alternate forms of the BNT, LFI and RBMT were used in the neuropsychological examination and the ALS-FTD-Cog. Test scores were considered abnormal when below the 5$^{th}$ percentile, demographically corrected. Cognitive impairment was defined according to the Strong criteria.[5] Therefore, only tests of fluency, language, executive functions and social cognition were taken into consideration. Participants were considered to be cognitively impaired when they had impaired letter fluency, or impairment on at least two non-overlapping executive functions tests or two non-overlapping language tests.[5]





***ECAS***

A subset of patients with ALS, diagnosed at the outpatient neurology clinic of the University Medical Center Utrecht, underwent the ECAS within three months of the administration of the ALS-FTD-Cog. The ECAS was administered by a trained member of the research team. The ECAS (13 items) consists of an ALS specific and ALS non-specific part. The ALS specific part consists of tests of language, fluency and executive functions. The ALS non-specific part consists of tests of memory and visuospatial functions. The two parts combined produce an ECAS total score. The ECAS was considered abnormal when below predefined cut-off values (ECAS total score ≤105 points and ECAS ALS specific score ≤77 points).[9]

***Other measures***

Behavioural impairment was assessed in all participants with the ALS-FTD-Questionnaire (ALS-FTD-Q) and the Motor Neuron Disease Behaviour scale (MiND-B).[23, 24] Disease severity and respiratory function were measured in ALS patients with the ALS functional rating scale – revised (ALSFRS-R) and forced vital capacity (FVC), respectively.[25] Affective symptoms were measured with the Hospital Anxiety and Depression Scale (HADS) in all participants.[26] For a detailed description of all measures, see supplemental material.

**Clinimetric evaluation of the ALS-FTD-Cog**

The gold standard for cognitive impairment was the neuropsychological examination. Cognitive impairment was defined as impaired letter fluency and/or impairment on at least two non-overlapping executive functions tests and/or two non-overlapping language tests, according to the Strong criteria.[5]

Tentative cut-off scores of the ALS-FTD-Cog were investigated by two means in patients with ALS:

1. The ALS-FTD-Cog was considered abnormal when ≥ 1 test was below the 5$^{th}$ percentile, demographically corrected. The sensitivity and specificity were calculated, as compared to the neuropsychological examination.
2. A ROC curve analysis was performed for the ALS-FTD-Cog mean T-score (mean of T-scores of all four items). Youden's J statistic was used to determine the optimal cut-off value.

For comparison, the sensitivity and specificity of the ECAS were calculated in a subset of patients with ALS, using cut-off scores as described above.[9]

Sensitivity and specificity of the ALS-FTD-Cog were also calculated in the bvFTD and healthy control group. We expected to find a high percentage of cognitive

impairment in the patients with bvFTD and a low percentage in the healthy control group.

We also assessed associations of the ALS-FTD-Cog with other measures. We therefore calculated correlations of the ALS-FTD-Cog with measures of cognition (NPE total score; i.e. the sum of T-scores of all items, the ECAS total score and the ECAS ALS specific score), behaviour (ALS-FTD-Q and MiND-B), physical impairment (ALSFRS-R and FVC) and affective symptoms (HADS).

### Statistical analysis

The sensitivity and specificity of the ALS-FTD-Cog, ECAS total score and ECAS ALS specific score were calculated by means of contingency tables. Furthermore, ROC curve analyses were performed of the ALS-FTD-Cog mean T-score, the ECAS total score and ECAS ALS specific score, and Youden's J statistic was calculated. The correlations between cognitive (ALS-FTD-Cog (mean T-score), NPE (total T-score), ECAS total score and ECAS ALS specific score), behavioural (ALS-FTD-Q and MiND-B) and other measures (ALSFRS-R, FVC, HADS anxiety and HADS depression) were expressed as Spearman rank correlation coefficients ($r_s$). Multiple imputation was performed with iterative Markov chain Monte Carlo method for missing neuropsychological test results (30/1524 data points (2.0%). Statistical significance level was set at $p$=0.05. Analyses were performed in PASW statistics, version 26 (SPSS).

## RESULTS

### Participants

We included 72 ALS patients, 21 bvFTD patients (of whom 5 had concurrent ALS) and 34 healthy controls (table 1 and supplemental material). A subset of 29 ALS patients (40.3%) had been administered the ECAS.

### Cognitive test results

Twenty ALS patients (27.8%) had cognitive impairment, based on the NPE and the Strong criteria, mostly in the social cognition (n=20) and executive functions (n=12) domains (supplemental material).

Thirty-two ALS patients (44.4%) were impaired on one (n=23) or more (n=9) tests of the ALS-FTD-Cog (supplemental material). The faux-pas test (social cognition) was most frequently impaired (n=28).





**Table 1.** Participant characteristics

| | ALS | | bvFTD | HC |
|---|---|---|---|---|
| | **Total (n=72)** | **ECAS sample (n=29/72)** | **(n=21)** | **(n=34)** |
| Age | 62.6 (10.0)* | 62.0 (8.7) | 64.6 (10.0)* | 58.4 (10.1) |
| Sex (m/f) | 50/22* | 20/9* | 17/4* | 14/20 |
| Education (years) | 14.0 (3.0) | 14.2 (2.6) | 14.5 (2.2) | 14.9 (1.9) |
| Disease duration (mo) | 9.0 (4-16) | 9.0 (5-13) | 29.0 (9-166) | n/a |
| Site of onset (l/b/lb) | 48/22/2 | 21/6/2 | n/a | n/a |
| ALSFRS-R | 40.0 (28-47) | 40.0 (30-47) | n/a | n/a |
| FVC (%pred) | 92.5 (15.8) | 93.8 (15.3) | n/a | n/a |
| HADS anxiety | 4.0 (0-13)* | 4.0 (0-12) | 5.0 (0-12) | 3.0 (0-7) |
| HADS depression | 2.0 (0-11)* | 2.0 (0-10) | 3.0 (0-8)* | 0.5 (0-8) |
| *C9orf72* mutation | 4^ | 2^ | 3^ | n/a |
| Survival (mo) | 25.5 (7-67)^^ | 27.0 (15-67) | n/a | n/a |
| ALS-FTD-Q | 13.3 (10.3)** | 9.3 (7.4) | 43.8 (12.7)** | 6.4 (6.8) |
| MiND-B# | 34.3 (3.0)* | 35.0 (1.5)* | 26.4 (6.3)** | 35.7 (0,8) |

Legend. Data are presented as mean (SD) or median (range), when appropriate. Mo: months; l: limb onset; b: bulbar onset; lb: both limb and bulbar onset; ALSFRS-R: ALS functional rating scale – revised; FVC (%pred): forced vital capacity, percentage of predicted value; n/a: not applicable. Statistical differences were examined between each of the patient groups and HC. *$p$<0.05; **$p$<0.001; ^C9orf72 mutation status was missing in 11 patients (total cohort), 2 patients (ECAS cohort) and 8 bvFTD patients. ^^To date (checked on 22 November 2020) 66 ALS patients are deceased. #ALS N=57, HC N=26, FTD N=19. The participants who were administered the ECAS were patients who visited the outpatient clinic of the University Medical Center Utrecht, and therefore can be considered a random (geographic) sample. The mean interval between the administration of the ALS-FTD-Cog and ECAS was 41 days (SD 25). A part of the current cohort has been published previously.[18]

Respectively nine and seven patients with ALS (out of 29, 31.0% and 24.1%) had an abnormal ECAS total score and ECAS ALS specific score. Five of these patients had cognitive impairment on the neuropsychological examination.

Eighteen patients with (ALS-)bvFTD (86%) had cognitive impairment based on the neuropsychological examination, mostly in the domains social cognition (n=18), executive functions (n=18) and verbal memory (n=15). Seventeen of these patients had an abnormal ALS-FTD-Cog. One healthy control (2.9%) had cognitive impairment based on the neuropsychological examination, in the domains social cognition and executive functions.

According to the ALS-FTD-Q, ten patients with ALS (13.9%) had mild behavioural impairment and six patients (8.3%) fulfilled criteria for bvFTD.[19] Twelve patients (out of 57, 21.1%) had behavioural impairment according to the MIND-B.[24]

**Test characteristics of the ALS-FTD-Cog**
The median administration time in ALS patients was 40 minutes (range 28-61). The scores on the subtests of the ALS-FTD-Cog are shown in the supplemental material for all participant groups.

***Sensitivity and specificity***
When ≥1 impaired test of the ALS-FTD-Cog was considered abnormal, the sensitivity and specificity in ALS patients using the NPE as gold standard were 65.0% and 63.5%, respectively (supplemental material). The sensitivity and specificity in (ALS-)bvFTD patients were 94.4% and 100%, respectively.

The ROC curve analysis of the ALS-FTD-Cog mean T-score showed an AUC of 0.72 (95% CI 0.58-0.86), with a Youden's J statistic of 0.4. The optimal cut-off value was 46.9, with a corresponding sensitivity of 65% and specificity of 75% (table 2).

The sensitivity of both the ECAS total score and ECAS ALS specific score was 83.3% in ALS patients, using the NPE as gold standard. The specificity of the ECAS total and ALS specific score in ALS patients was 82.6% and 91.3%, respectively (supplemental material). The ROC curve analyses of the ECAS total score and ECAS ALS specific score showed an AUC of 0.90 (95% CI 0.78-1.01) and 0.95 (95% CI 0.86-1.03), respectively, with a Youden's J statistic of 0.83 and 0.78, respectively (table 2).

**Table 2.** ROC curve analysis and Youden's J statistic of the ALS-FTD-Cog and ECAS

| | | ALS (n=74) | ALS (n=29) | bvFTD (n=21) | HC (n=34) |
|---|---|---|---|---|---|
| ALS-FTD-Cog mean T-score | AUC | 0.72 (0.58-0.86) | 0.60 (0.30-0.90) | 0.78 (0.56-0.99) | 0.61 (0.44-0.77) |
| | Youden's J | 0.4 | 0.33 | 0.61 | 0.61 |
| ECAS total | AUC | n/a | 0.90 (0.78-1.01) | n/a | n/a |
| | Youden's J | n/a | 0.83 | n/a | n/a |
| ECAS ALS specific | AUC | n/a | 0.95 (0.86-1.03) | n/a | n/a |
| | Youden's J | n/a | 0.78 | n/a | n/a |

Legend. ALS-FTD-Cog: amyotrophic lateral sclerosis – frontotemporal dementia – cognitive screen; ECAS: Edinburgh cognitive and behavioural ALS screen; ALS: amyotrophic laterals sclerosis; bvFTD: behavioural variant frontotemporal dementia; HC: healthy controls; AUC: area under the curve. Youden's J statistic is calculated with the formula sensitivity + specificity – 1.





***Associations of ALS-FTD-Cog with measures of cognition, behaviour, physical impairment and affective symptoms***
The correlation of the ALS-FTD-Cog scores with the NPE was moderate ($r_s$ 0.54, p<0.001) and weak with the ECAS total score and ECAS ALS specific score ($r_s$ 0.34, $p$=0.08 and $r_s$ 0.25, $p$=0.2, respectively. The correlation of the NPE with the ECAS total score and ALS specific score was moderate ($r_s$ 0.51 and $r_s$ 0.49, respectively, $p$<0.01). Correlations of the ALS-FTD-Cog scores with the ALS-FTD-Q, ALSFRS-R, FVC, HADS anxiety and HADS depression were weak (supplementary material).

## DISCUSSION

We investigated the clinical validity of a new cognitive screening tool, the ALS-FTD-Cog in a cohort of ALS patients with a short disease duration (symptom onset <12 months) with a prevalence of cognitive impairment of nearly 30%, which is comparable to large population based cohort studies.[27, 28] The sensitivity and specificity of the ALS-FTD-Cog in ALS patients were moderate and do not justify its use in clinical practice. The sensitivity and specificity of the ALS-FTD-Cog in bvFTD patients were high, indicating that the screen detects cognitive impairment as seen in bvFTD. In a subset of 29 patients, a high sensitivity and specificity of another, widely used cognitive screening instrument, the ECAS, was found.

**Screening for cognitive impairment**
A screening test should be easy to administer and score, widely applicable, time-efficient with a high sensitivity to select patients who may need further testing, and a high specificity to preclude unnecessary further testing. The ALS-FTD-Cog is easy to administer although basic training in administering and scoring of cognitive tests is needed. The ALS-FTD-Cog is widely applicable as it is composed of internationally validated tests with available normative data. The administration time is quite long (40 minutes) which is similar to the ECAS.[12]

However, the moderate sensitivity of the ALS-FTD-Cog (65%) indicates that it is less suitable as a screening tool. This could be caused by multiple factors. First, we might have included the wrong tests in the screen. The faux pas test, a measure of theory of mind, proved difficult to interpret for both the participant and the administrator. In our study most participants, including healthy controls, had problems attributing only one emotion to the situation at hand. This led to a high number of abnormal empathy scores. When we would have excluded the empathy score from the screen and only consider the faux pas total score, this would have resulted in a decrease of the sensitivity. A recent

study of social cognition in bvFTD and other neurodegenerative and psychiatric disorders found that the faux pas test does not differentiate bvFTD patients from the other participant groups. However, the Ekman 60 faces test, which was included in our NPE, but not in the screen, showed a high discriminating rate in a previous study.[29] The discriminating rate of the Ekman 60 faces test was also shown in a meta-analysis, comparing patients with bvFTD to patients with Alzheimer's disease and healthy controls.[30] In ALS, especially the recognition of disgust and surprise seems impaired.[22]

Another test that may have caused a limited sensitivity of our screen is the Rivermead behavioural memory test (RBMT). The current consensus criteria for cognitive impairment in ALS do not include memory impairment.[5] Our selection of tests was based on our meta-analysis of the cognitive profile of ALS that showed a large effect size for verbal memory impairment and evidence from multiple imaging and pathological studies showing hippocampal involvement in ALS.[13, 31-34] In the current study, the RBMT was abnormal in 8 patients (11.1%), of whom 7 also had abnormal tests in the executive domain, which reflects the low prevalence of isolated memory impairment in ALS.[28] Thus, the RBMT had limited added value for the detection of cognitive impairment in ALS, although it increases the internal consistency of the screen.

Second, the moderate clinimetric properties of the ALS-FTD-Cog might be related to the inclusion of a limited number of tests. We included four complete neuropsychological tests in the ALS-FTD-Cog, instead of a higher number of separate items of (sub)tests, hypothesizing that the availability of demographically corrected normative data would result in feasibility (no need to generate new normative scores) and a high sensitivity. In comparison, the ECAS includes separate items of 13 neuropsychological tests.[9] This approach leads to the investigation of different facets of multiple cognitive domains, of which the potential benefit, i.e. a higher sensitivity, has been suggested previously.[12] However, the scoring of such a screening tool is not based on established normative data and the weight of the scores of the different tests is seemingly random. The reported sensitivity and specificity of the ECAS range between 50-100% and 80-95%, respectively.[12, 35-37] In our small study population, the previously reported high sensitivity of the ECAS was confirmed when using the original cut-off values. In combination with previous studies which have shown good clinimetric properties of the ECAS our results indicate that the ECAS is a valid screening instrument for cognitive impairment in ALS.

### Limitations

Less than half of the ALS patients were administered the ECAS (40.3%), because it was not yet published at the beginning of our study. Also, a small minority





of participants had missing data on the neuropsychological examination for which multiple imputation was used.

## CONCLUSION

The ALS-FTD-Cog had a moderate sensitivity and specificity in our cohort of patients with ALS, when compared to the gold standard and we do not recommend its clinical use in patients with ALS, although the clinimetric properties in bvFTD patients are excellent. Regarding the ECAS, we were able to corroborate a previously reported high sensitivity and specificity in a small subset of patients, indicating that it is a valid screening tool for cognitive impairment in ALS.

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## SUPPLEMENTAL MATERIAL

**Table 1.** Neuropsychological examination

| Order | Cognitive test | Cognitive domain | Items (N) | Parallel version |
|---|---|---|---|---|
| 1 | Dutch adult reading test (DART) | Verbal IQ | 50 | No |
| 2 | Benton temporal orientation test (BTOT) | Global cognition | 5 | No |
| 3 | Anti-saccade test | Executive functions | 20 | No |
| 4 | Similarities (subtest of WAIS-IV) | Language | 19 | No |
| 5 | Boston naming test (BNT) | Language | 20 | Yes |
| 6 | Judgment of line orientation (JOLO) | Visuospatial functions | 30 | No |
| 7 | Letter fluency index | Executive functions | n/a | Yes |
| 8 | Category fluency (animals, occupation, supermarket) | Executive functions | n/a | No |
| 9 | Visual association test | Visual memory | 12 or 24 | No |
| 10 | Rey auditory verbal learning test (RAVLT) | Verbal memory | 7 | Yes |
| 11 | Letter Number sequencing | Attention | 10 | No |
| 12 | Rivermead behavioral memory test (RBMT) | Verbal memory | 2 | Yes |
| 13 | Ekman 60 faces test | Social cognition | 60 | No |
| 14 | Wisconsin card sorting test (WCST) | Executive functions | n/a | No |

Legend. The neuropsychological test protocol was always performed in this order. Breaks were given when needed. For the determination of cognitive impairment, the following tests were used: anti-saccade test, similarities, Boston naming test, letter fluency index, category fluency, letter number sequencing, Ekman 60 faces test and the Wisconsin card sorting test.

### Other measures

For all participants the proxy filled out the ALS-FTD-Questionnaire (ALS-FTD-Q) and the Motor neuron disease behaviour scale (MiND-B), two disease specific and validated questionnaires for behavioural changes in ALS.[1, 2] A score between 22 and 28 on the ALS-FTD-Q (maximum score 100) indicates mild behavioural impairment, a score of ≥29 indicates severe behavioural impairment, consistent with bvFTD. A score below 34 on the MiND-B (maximum score 36) indicates behavioural impairment (without a distinction of mild and severe impairment). Disease severity was measured in ALS patients with the ALS functional rating scale – revised (ALSFRS-R, score ranges from 0 to 48; a higher score indicates less impairment).[3] Respiratory function was assessed with the upright forced vital capacity (FVC) in ALS patients. Symptoms of anxiety and depression were measured with the Hospital Anxiety and Depression Scale (HADS) in

all participants. One item ('I feel slowed down') was excluded, as described previously (score ranges from 0 to 39; a higher score indicates more anxiety/depression).[1, 4]

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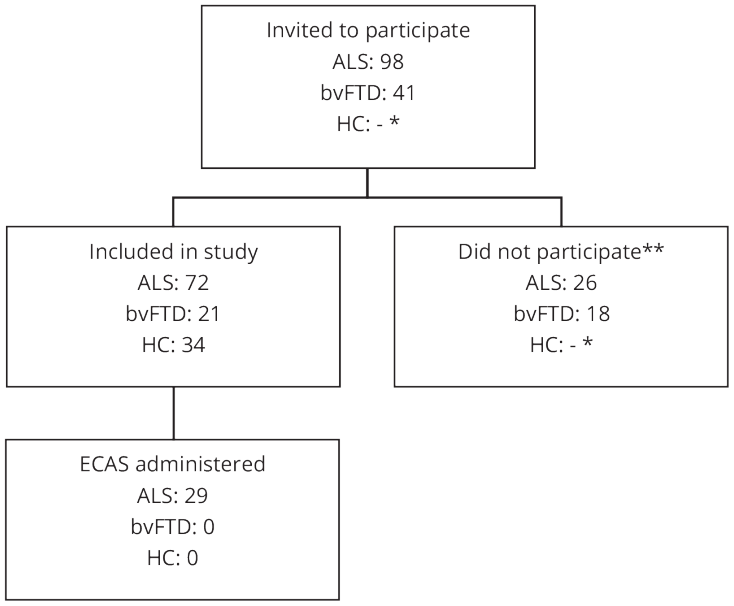
**Figure 1.** Flowchart of participant selection




Legend. ALS: amyotrophic lateral sclerosis patients; bvFTD: behavioural variant frontotemporal dementia patients. This group also included 5 ALS-bvFTD patients; HC: healthy controls; ECAS: Edinburgh cognitive and behavioral ALS screen. *Healthy controls were approached through social media platforms. **Reasons to decline participation were fatigue (n=11), lack of interest (n=10) and fast progression of motor impairment (n=5).





**Table 2.** Demographically corrected scores on the ALS-FTD-Cog per participant category

| | ALS (N=72) | bvFTD (N=21) | HC (N=34) |
|---|---|---|---|
| **Faux pas test** | 48.5 (15.3) | 26.0 (20.8)** | 46.5 (8.4) |
| Total score | 34.2 (15.5)* | 12.3 (12.5)** | 41.6 (13.2) |
| Empathy score | | | |
| **RBMT** | 46.5 (8.4) | 28.1 (11.6)** | 49.0 (9.8) |
| Immediate | 47.2 (11.2) | 26.3 (26.8)** | 49.2 (9.3) |
| Delayed - corrected | | | |
| **LFI** | 43.7 (6.4)* | 14.9 (60.7)** | 40.4 (3.2) |
| **BNT** | 48.6 (9.5) | 35.8 (12.8)** | 49.6 (7.8) |

Legend. Scores of the neuropsychological tests are T-scores, shown as mean (SD). RBMT: Rivermead behavioural memory test – story recall; immediate: immediate recall; delayed – corrected: delayed recall, corrected for immediate recall score; LFI: letter fluency index; BNT: Boston naming test. Differences were examined between ALS and HC, bvFTD and HC and ALS and bvFTD. *p<0.05; **p<0.001. All test scores differed significantly between ALS and bvFTD and bvFTD and HC.

**Figure 2.** ROC curve analysis of the ALS-FTD-Cog and ECAS in 29 patients with ALS

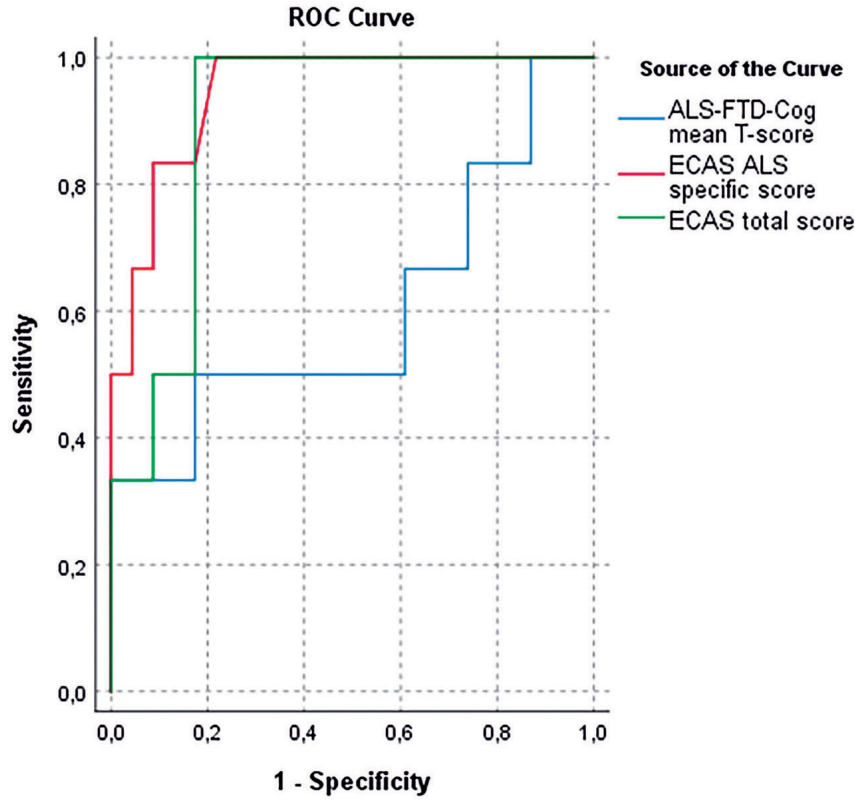


**Table 3a.** Contingency table of ALS-FTD-Cog in ALS patients, compared to the neuropsychological examination

| | NPE + | NPE – | N |
|---|---|---|---|
| ALS-FTD-Cog + | 13 | 19 | 32 |
| ALS-FTD-Cog – | 7 | 33 | 40 |
| N | 20 | 52 | 72 |

Legend. ALS-FTD-Cog: ALS – FTD cognitive screen; NPE: neuropsychological examination; –: normal test results; +: abnormal test results. When only the total score of the faux pas test (instead of the empathy score) was taken into consideration, the number of patients with a normal ALS-FTD-Cog increased to 55, with a sensitivity and specificity of 50% and 86.5%, respectively, compared to the neuropsychological examination. Youden's J statistic = 0.29.

**Table 3b.** Contingency table of ECAS total score in ALS patients, compared to the neuropsychological examination

| | NPE + | NPE – | N |
|---|---|---|---|
| ECAS total + | 5 | 4 | 9 |
| ECAS total – | 1 | 19 | 20 |
| N | 6 | 23 | 29 |

Legend. ECAS: Edinburgh cognitive and behavioural ALS screen; NPE: neuropsychological examination; –: normal test results; +: abnormal test results. Youden's J statistic = 0.66.

**Table 3c.** Contingency table of ECAS ALS specific score in ALS patients, compared to the neuropsychological examination

| | NPE + | NPE – | N |
|---|---|---|---|
| ECAS ALS specific + | 5 | 2 | 7 |
| ECAS ALS specific – | 1 | 21 | 22 |
| N | 6 | 23 | 29 |

Legend. ECAS: Edinburgh cognitive and behavioural ALS screen; NPE: neuropsychological examination; –: normal test results; +: abnormal test results. Youden's J statistic = 0.75.

**Table 4.** Spearman rank correlation coefficients of all cognitive measures in ALS patients

| | ALS-FTD-Cog | ECAS Total | ECAS ALS specific | ECAS not specific |
|---|---|---|---|---|
| NPE | 0.55** | 0.51** | 0.49** | 0.49** |
| ALS-FTD-Cog | - | 0.34 | 0.25 | 0.46* |

Legend. Correlations are expressed as Spearman rank correlation coefficients ($r_s$). NPE: neuropsychological examination (sum of T-scores); ALS-FTD-Cog: ALS-FTD cognitive screen (mean T-score); ECAS: Edinburgh cognitive and behavioural ALS screen. *$p$< 0.05, **$p$< 0.01





**Table 5.** Spearman rank correlation coefficients of ALS-FTD-Cog with other measures in ALS patients

| | ALS-FTD-Q | MiND-B | ALSFRS-R | FVC | HADS anxiety | HADS depression |
|---|---|---|---|---|---|---|
| ALS-FTD-Cog | -0.32* | 0.18 | 0.02 | 0.11 | -0.15 | -0.19 |

Legend. Correlations are expressed as Spearman rank correlation coefficients ($r_s$). ALS-FTD-Cog: ALS-FTD cognitive screen (mean T-score); ALS-FTD-Q: amyotrophic lateral sclerosis – frontotemporal dementia – questionnaire; MiND-B: Motor neuron disease – behavioural questionnaire; ALSFRS-R: ALS functional rating scale – revised; FVC: forced vital capacity; HADS: hospital anxiety and depression scale. *$p$< 0.01

**Table 6.** ALS patients (n=29) impaired on subtests of the ECAS and ALS-FTD-Cog

| Cognitive domain | Impaired on ECAS (%) | Impaired on ALS-FTD-Cog (%) |
|---|---|---|
| Language | 14 (48.3%) | 1 (3.4%) |
| Fluency | 2 (6.9%) | 1 (3.4%) |
| Executive functions | 9 (31.0%) | 11 (37.9%)* |
| Memory | 4 (13.8%) | 5 (17.2%) |
| Visuospatial | 4 (13.8%) | n/a |
| ALS specific score | 7 (24.1%) | n/a |
| Total score | 9 (31.0%) | n/a |

Legend. ECAS: Edinburgh cognitive and behavioural ALS screen; ALS-FTD-Cog: ALS-FTD-cognitive screen. *The faux pas test is a measure of social cognition, which is a part of the executive functions domain in the ECAS.

# 7

## The ALS-FTD-Q: A new screening tool for behavioural disturbances in ALS

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## ABSTRACT

### Objective
The assessment of behavioural disturbances in amyotrophic lateral sclerosis (ALS) is important because of the overlap with the behavioural variant of frontotemporal dementia (ALS-bvFTD). Motor symptoms and dysarthria are not taken into account in currently used behavioural questionnaires. We examined the clinimetric properties of a new behavioural questionnaire for patients with ALS (Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire [ALS-FTD-Q]).

### Methods
In addition to other clinimetric properties, we examined reliability, clinical validity, and construct validity of the ALS-FTD-Q, using data from patients with ALS (n = 103), ALS-bvFTD (n = 10), bvFTD (n = 25), muscle disease control subjects (n = 39), and control subjects (n = 31). Construct validity of the ALS-FTD-Q was assessed using the Frontal Systems Behavior scale (FrSBe), Frontal Behavioral Inventory (FBI), Hospital Anxiety and Depression Scale, ALS Functional Rating Scale - Revised, Frontal Assessment Battery, Mini-Mental State Examination, and a fluency index. In addition, the point prevalence of behavioural disturbances according to the ALSFTD-Q was compared with those obtained with the FrSBe and FBI.

### Results
The internal consistency of the ALS-FTD-Q was good (Cronbach α = 0.92). The ALS-FTD-Q showed construct validity because it correlated highly with other behavioural measures ($r$ = 0.80 and 0.79), moderately with measures of frontal functions and global cognitive functioning ($r$ = 0.37; $r$ = 0.32), and poorly with anxiety/depression and motor impairment ($r$ = 0.18 for both). The ALS-FTD-Q discriminated between patients with ALS-bvFTD, patients with ALS, and control subjects. The point prevalence of behavioural disturbances in patients with ALS measured with the ALS-FTD-Q was lower than that for the FrSBe and FBI.

### Conclusion
The ALS-FTD-Q is a feasible and clinimetrically validated instrument for the screening of behavioural disturbances in ALS.






## INTRODUCTION

The frontotemporal brain regions are affected in a proportion of patients with amyotrophic lateral sclerosis (ALS).[1-3] Clinically, this may lead to the behavioural variant of frontotemporal dementia (bvFTD) (in 5%–10% of patients with ALS), mild frontotemporal cognitive deficits (in 32%–45% of patients with ALS), or mild behavioural disturbances in patients with ALS.[4-8] These nonmotor changes in patients with ALS may negatively influence survival and hinder adherence to therapeutic interventions and relations with caregivers.[9-11]

The gold standard for behavioural disturbances is a detailed family interview. When this is not feasible, a neuropsychiatric screening instrument is an alternative. Importantly, the scoring of items should not be influenced by muscle weakness, dysarthria, or pseudobulbar affect, as these may overestimate behavioural disturbances in patients with ALS.[12]

The neuropsychiatric instruments currently available for assessing behaviour have not been validated in patients with ALS and contain several items that rely on the ability to speak, eat, and move without problems.[13-15] To overcome these issues, we investigated the clinimetric properties of a new screening tool, the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire (ALS-FTD-Q), for the detection of bvFTD and mild behavioural disturbances in ALS.



## METHODS

### Subjects
Five groups of patients were recruited from tertiary referral centres for ALS and dementia, all in the Netherlands: 103 patients with ALS (possible, probable, or definite ALS according to the El Escorial criteria)[16]; 10 patients with ALS-bvFTD who had the diagnosis of ALS-bvFTD by the treating clinician before this study, according to the El Escorial[16] and Neary criteria[17]; 25 patients with bvFTD without ALS that had been diagnosed before the study, according to the Neary criteria[17]; 39 patients with muscle diseases (muscle controls) (inclusion body myositis [n = 10], limb girdle dystrophy 2A [n = 8], oculopharyngeal muscular dystrophy [n = 6], Miyoshi myopathy [n = 9], and ALS mimics [n = 6]); and 31 subjects evaluated at the outpatient neurology clinic for diverging symptoms (e.g. sensory symptoms, tremor, and headache) (other controls). These subjects had no medical history of muscle disease, CNS disorder, or psychiatric disorder. The patients with ALS-bvFTD and bvFTD served as positive controls (n = 35);

the patients with muscle diseases and the other controls served as negative controls (n = 70).

Only patients with a proxy were included. A proxy can be a partner, parent, sibling, adult child, or other caregiver who is able to assess the patient's behaviour. In 1.6% of the patients contacted, absence of a proxy was the reason not to participate. Patients and control subjects were excluded if they did not speak Dutch fluently or if they had (a history of) a psychiatric disorder or a neurologic disease with CNS involvement.

**Standard protocol approvals, registrations and patient consents**
The local ethics committees of the participating hospitals approved the study. Written informed consent was obtained from all subjects.

**ALS-FTD-Q**
The ALS-FTD-Q (appendix e-1 on the *Neurology*® website at www.neurology.org and on www.alsftdq.nl) is an observer report scale aimed at the proxy of a patient with ALS. Items for the ALS-FTD-Q were taken from a systematic review of neurobehavioural symptoms (i.e. behavioural, cognitive, and psychiatric disturbances) in 170 published patients with motor neuron disease and bvFTD[18], and the item selection was mainly based on the pooled prevalence rates of neurobehavioural symptoms in the review. The phrasing of the items was adjusted for motor and speech dysfunction. Face validity of the ALS-FTD-Q is described in appendix e-2. The ALS-FTD-Q has 25 items (including 3 cognitive items: memory, concentration, and orientation in time), with a 4-point rating scale; the maximum score of the ALS-FTD-Q is 100. A higher score indicates more behavioural disturbances. The time required to complete the questionnaire was estimated to be between 5 and 10 minutes.

**Procedure**
Most patients with ALS were visited at home (n = 97, including 9 patients with ALS-bvFTD). The proxy was requested to fill in the ALS-FTD-Q and 2 other behavioural scales (for instruments, see below) in a separate room while the patient underwent a short battery of tests that assessed cognitive and affective functions and functional motor status. Proxies of 16 consecutive patients with ALS (including 1 patient with ALS-bvFTD) filled in the ALS-FTD-Q during an outpatient clinic visit, separate from the home-visit study.

Proxies of the other patients and control subjects filled in the ALS-FTD-Q at the outpatient clinics during a regular visit, in a room separated from the patient.





**Instruments used in the home-visit study**
The proxy assessed the behaviour of the patient with the ALS-FTD-Q and the Frontal Systems Behavior Scale (FrSBe), a 46-item behaviour scale with carer ratings of premorbid and postmorbid behaviour in the domains of apathy, executive dysfunction, and disinhibition[14], and the Frontal Behavioral Inventory (FBI), a 24-item scale measuring frontal lobe-mediated behaviour.[15]

The patient was administered the Mini-Mental State Examination (MMSE)[19]; the Frontal Assessment Battery (FAB), a 6-item instrument measuring frontal lobe functions, e.g. conceptualization and perseveration[20]; letter (D, A, T) and category (animals and occupations) fluency, measures of executive function with correction for speech/motor dysfunction by calculating a mean thinking time per word in seconds (fluency index)[12, 21] (written or spoken versions were used, depending on disability); the Hospital Anxiety and Depression Scale (HADS), a 14-item scale[22]; and the ALS Functional Rating Scale-Revised (ALSFRS-R), a 12-item questionnaire for motor dysfunction in ALS.[23]

Patients in whom impaired manual dexterity precluded performance of the "writing a sentence" item of the MMSE were allowed to say the sentence, provided their speech was intelligible. For other items that require manual dexterity, e.g. "intersecting pentagons" of the MMSE and 5 of the 6 items of the FAB, a note was made when these tasks could not be performed. We recorded the score obtained and the highest obtainable score. The highest obtainable score is the score if all items are done perfectly, leaving out the items missed due to motor impairment. Extrapolated scores of the MMSE and FAB were used for analyses, according to the formula: *extrapolated score = score obtained x maximum scale score/highest obtainable score for this patient.* A higher extrapolated score means a better performance. Disease onset was defined as the month when the first sign of muscle weakness (ALS) or behavioural changes (bvFTD) was noted. Bulbar involvement was defined as a score ≤11 on the 3 bulbar items of the ALSFRS-R.

**Clinimetric evaluation of ALS-FTD-Q**
The following clinimetric properties of the ALS-FTD-Q were studied: reliability (both internal consistency and test-retest reliability), construct validity, clinical validity, and the presence of a floor and ceiling effect.

Internal consistency refers to the statistical coherence of the scale items and can be measured by the Cronbach α coefficient, which is based on the weighted average correlation of items within a scale. Internal consistency is considered to be good if $\alpha \geq 0.80$. We calculated item-total correlations, which represent the correlation of a single item with the sum of all other scale items. Correlations ≥

0.30 were considered to be sufficient. Test-retest reliability was investigated in a pilot study on the proxies of 17 patients with ALS, including 4 patients with ALS-bvFTD (appendix e-2).

**Table 1.** Demographic and clinical characteristics of the patients with ALS and positive and negative control subjects assessed with the ALS-FTD-Q

| | | Positive control subjects | | Negative control subjects | |
|---|---|---|---|---|---|
| | **ALS (n = 103)** | **ALS-bvFTD (n=10)** | **bvFTD (n=25)** | **Muscle disease (n = 39)** | **Other controls (n = 31)** |
| Age, y, mean (SD) | 61.4 (11.9) | 60.2 (10.4) | 63.4 (6.4) | 58.7 (13.3) | 58.3 (11.7) |
| Sex, M/F | 73/30 | 7/3 | 17/8 | 22/17 | 15/16 |
| Limb/bulbar onset, n | 89/14 | 4/6 | | | |
| Bulbar involvement, %[a] | 60.2 | 100 | | 38.5 | |
| Disease duration, mo, median (range) | 33.5 (4-328) | 35.5 (0-80) | 48 (13-355) | 153 (12-519) | |
| ALSFRS-R[b] | 31.5 (9.2) | 32.9 (6.1) | | | |

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale – Revised; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire; bvFTD = behavioural variant of frontotemporal dementia.
[a] Bulbar involvement was defined as a score ≤11 on the 3 bulbar items of the ALSFRS-R.
[b] The maximum score of the ALSFRS-R is 48 and indicates no motor dysfunction.

Construct validity was assessed in the group of 97 patients with ALS (including 9 patients with ALS-bvFTD) who underwent multiple tests at home. We measured the extent to which the ALS-FTD-Q correlates with measures that address the same concept (i.e. frontal behaviour) and measures that address different concepts. We assumed that for the ALS-FTD-Q to be valid, the ALS-FTD-Q scores had to show high correlations with the other frontal behaviour scale scores (FrSBe and FBI), moderate correlations with frontal lobe functions (FAB and fluency) and global cognitive functions (MMSE), and low correlations with affective functions (HADS) and motor functions (ALSFRS-R).

A scale demonstrates clinical validity if it discriminates between groups of patients with known differences in clinical status (i.e. ALS without bvFTD vs bvFTD with or without ALS). Floor and ceiling effects of the ALS-FTD-Q were analysed (percentage of patients with a minimum and maximum score).

**ALS-FTD-Q vs comparable scales**

To explore whether the results of the ALS-FTD-Q differ from scales that are currently used in patients with ALS, we compared point prevalences of abnormal behaviour assessed with the ALS-FTD-Q (using tentative cut-off





scores derived from our negative and positive control groups) with those from the FrSBe and the FBI (using published cut-off scores). We aimed to compare the ALS-FTD-Q scores with scores of the other scales for both mildly and severely abnormal behaviour, because a spectrum of behavioural disturbances in ALS has been suggested in earlier studies.[24, 25] The cut-off of the ALS-FTD-Q indicating mild disturbances (below which behaviour is normal) was based on the 95th percentile of the 70 negative controls. The cut-off indicating severe disturbances (in the bvFTD range) was based on the lowest ALS-FTD-Q score in the group of 35 positive control subjects (patents with bvFTD and ALS-bvFTD). For the comparison with other scales, for mild disturbances we used the cut-off score of the FrSBe (*t* score >65; >1.5 SD above the mean)[14], and for severe disturbances we used the published cut-off score of the FBI.[15] We assessed performance on the ALS-FTD-Q in patients with incident and prevalent disease. Patients with incident disease were defined as being assessed within 1 year from the diagnosis.[9]

**Statistical analysis**

Internal consistency of the ALS-FTD-Q scores was expressed as Cronbach α coefficient. Item-total correlations and test-retest correlations were expressed as Pearson correlation coefficients (*r*) and intraclass correlation coefficients, respectively. Associations between the ALS-FTD-Q scores and the other measures were expressed as Spearman rank correlation coefficients ($r_s$). Differences between ALS-FTD-Q scores and patient characteristics in relation to the various subgroups were analysed using the Mann-Whitney *U* test, Kruskal-Wallis test, or $X^2$ test. Statistical significance level was set at $p = 0.05$. Analyses were performed in PASW statistics, version 18 (SPSS).

## RESULTS

We included 113 patients with ALS (80 male [70.8%]), 10 of whom were diagnosed with ALS-bvFTD before the study. The mean age at examination was 61.3 years (SD 11.7), and the median disease duration was 2.8 years (34 months, range 4 –328 months) (table 1). Ninety-three patients (82.3%) had limb-onset ALS. Bulbar involvement was present in 72 patients (63.7%). Gender and age were not different among any of the groups.

**Clinimetrics**

The ALS-FTD-Q scores showed substantial internal consistency (Cronbach α = 0.92), and 23 of the 25 items showed an item-total score correlation ranging between 0.31 and 0.78. Two items (hypersexuality and euphoria) had an item-total score correlation of 0.20 and 0.26. The test-retest intraclass correlation of

the ALS-FTD-Q total score was 0.89 (n = 17; mean time between 2 assessments 65 days [SD 26.7]) (additional data for the test-retest group are given in appendix e-2). Construct validity was shown by high correlations between the ALS-FTD-Q and the FrSBe and FBI, moderate correlations with the FAB, fluency, and MMSE, and low correlations with the HADS and ALSFRS-R (table 2, figure 1). There was a floor effect (16 of 208 patients [7.7%] had a minimum score of 0); no ceiling effect was observed.

With regard to clinical validity, the median ALSFTD-Q score of patients with ALS without bvFTD (9, range 0–46) was lower than those for either patients with ALS-bvFTD (42, range 30–56) or patients with bvFTD (50, range 29–68) and higher than those for the muscle disease control group (6, range 0–24) and the other control subjects (5, range 0–20) (figure 2).

**Figure 1.** Correlations between the ALS-FTD-Q, the Frontal Behavioral Inventory (FBI) (r = 0.79; red), and the Frontal Systems Behavior scale (FrSBe) (r = 0.80; blue)

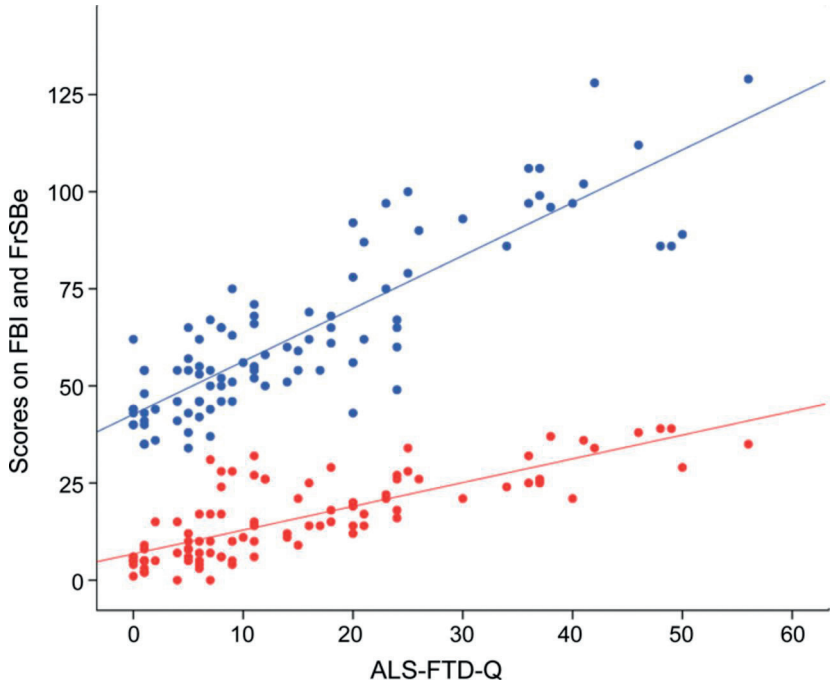







**Table 2.** Test scores and correlations of the ALS-FTD-Q with other measures of behavioural, cognitive, affective, and motor functions in patients with ALS

| | No. | Test score, median (range) | Correlation with ALS-FTD-Q[a] |
|---|---|---|---|
| **ALS-FTD-Q** | 97 | 11 (0-56) | |
| **Frontal behavioural symptoms** | | | |
| FrSBe | 95 | 56 (34-129) | 0.80 |
| FBI | 92 | 14 (0-39) | 0.79 |
| **Frontal/executive functions** | | | |
| FAB | 92 | 16 (3-18) | -0.37[b,c] |
| Fluency[d] | 92 | 5.6 (1.9-24.3) | 0.30 |
| **Cognitive functions** | | | |
| MMSE | 97 | 26.8 (9-30) | -0.32[b,c] |
| **Affective functions** | | | |
| HADS | 85 | 6 (0-24) | 0.18 |
| **Motor functions** | | | |
| ALSFRS-R | 97 | 33.0 (8-47) | -0.18[b] |

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire; FAB = Frontal Assessment Battery; FBI = Frontal Behavioral Inventory; FrSBe = Frontal Systems Behavior scale; HADS = Hospital Anxiety and Depression Scale; MMSE = Mini-Mental State Examination.

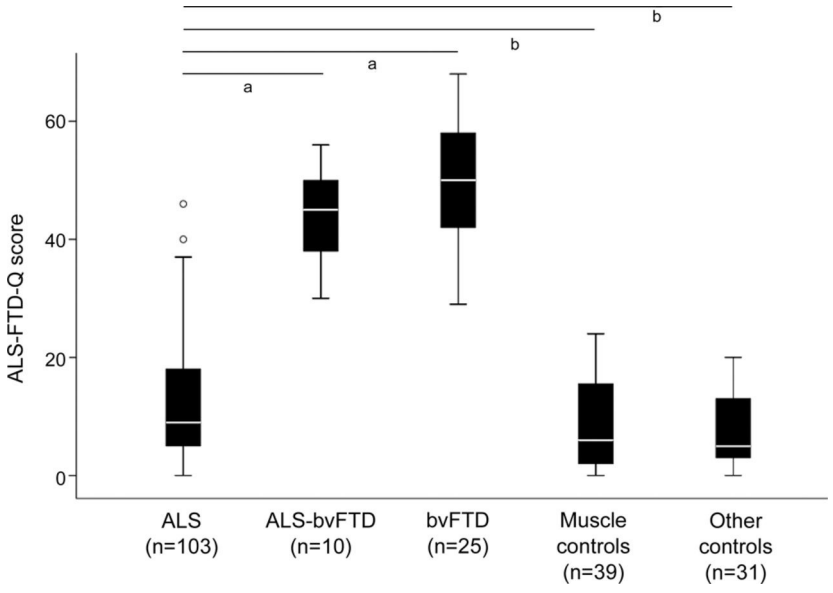
[a] Correlation values are expressed as Spearman correlation coefficients.

[b] Negative as higher scores on the FAB, MMSE, and ALSFRS-R indicate better performance.

[c] Extrapolated scores of the MMSE and FAB were used, corrected for missed items due to motor impairment.

[d] Fluency represents the letter fluency index (correlation coefficient for category fluency index = 0.30).

**Figure 2.** Boxplot with ALS-FTD-Q scores by diagnosis




[a]$p < 0.0001$; [b]$p < 0.05$, Mann-Whitney *U* Test. ALS = amyotrophic lateral sclerosis; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire; bv-FTD = behavioural variant of frontotemporal dementia.

### ALS-FTD-Q and comparable scales

Based on our scoring algorithm (Methods section), the ALSFTD-Q cut-off indicating mild disturbances was set at ≥22; the cut-off indicating severe disturbances (in the bvFTD range) was set at ≥29. In patients without a prior diagnosis of bvFTD who had complete data for the 3 behavioural scales (n = 86), mild and severe behavioural disturbances were shown in 11 (10.7%) and 7 patients (6.8%), respectively, with the ALS-FTD-Q. In comparison, according to the FrSBe and FBI, 16 patients (18.6%) had mild behavioural disturbances and 12 patients (14%) had severe behavioural changes. Of the 103 patients who were assessed with the ALS-FTD-Q, 27 (26.2%) were assessed within 1 year of the diagnosis (patients with incident disease), of whom 4 (14.8%) scored in the mild range and 1 in the severe range on the ALS-FTD-Q. The proportion of those with mild behavioural disturbances of the patients with incident disease was not significantly different from that of patients with prevalent disease ($X^2$ test; not analysed for severe behavioural disturbances).





## DISCUSSION

This study shows the clinimetric properties of a new screening instrument for behavioural disturbances, which was constructed to avoid bias due to motor and speech impairment in patients with ALS. The ALS-FTD-Q showed substantial internal consistency and test-retest reliability and both construct and clinical validity. Construct validity was shown by high correlations of the ALS-FTD-Q with frontal behavioural scales (same construct), intermediate correlations with frontal cognitive functions (related construct), and low correlations with anxiety/depression and motor function (not related constructs). The intermediate correlation between fluency and the ALS-FTD-Q in our study is comparable to findings by others and shows that the questionnaire measures a construct (frontal-mediated behaviour) that is related to fluency, supporting the construct validity of the ALS-FTD-Q.[26] In addition, clinical validity was shown because the ALS-FTD-Q discriminated between patients with a known difference in the presence of frontal behavioural disturbances. These good clinimetric properties and the easy way of administering the ALS-FTD-Q make it a feasible screening instrument in clinical practice as well as for research projects.

The assessment of behavioural changes and especially bvFTD in patients with ALS is important in clinical practice because bvFTD hinders adherence to therapeutic interventions and may negatively influence survival. In addition, bvFTD has a great impact on the relation of patients with ALS with their caregivers.[9-11]

To our knowledge, 3 screening instruments for nonmotor involvement (focusing on cognitive functions) have been investigated in patients with ALS.[27-29] One screen contains 15 questions about behaviour[27]; 2 other screens included the FBI.[28, 29] Compared with these screening instruments, the ALS-FTD-Q has 4 unique advantages. First, behavioural items were selected from a systematic review of case descriptions of 170 patients with ALS-bvFTD. Second, the phrasing of items was adjusted to take motor and speech dysfunction into account. This was done to minimize overestimation of behavioural disturbances due to motor impairment. Third, the ALS-FTD-Q has good clinimetric properties including internal consistency, construct validity, and clinical validity. Fourth, test scores were compared with both negative and positive control groups. The point prevalence of severe and mild behavioural disturbances according to the ALS-FTD-Q in our patients with ALS without a prior diagnosis of bvFTD is lower compared with the FBI (severe) and the FrSBe (mild behavioural changes). Our data may suggest that the FrSBe and FBI could overestimate behavioural disturbances in patients with ALS (because of bias due to motor symptoms and dysarthria). The alternative explanation, i.e. a low sensitivity of the ALS-

FTD-Q, is less likely for 3 reasons. First, we carefully selected items based on a systematic review to capture the full range of neurobehavioural changes known to occur in ALS, including delusions (paranoia), hallucinations, apathy, and eating disturbances, which were recently found to be prominent in patients with bvFTD with ALS.[18, 30, 31] Second, our cut-off included all the patients with a prior diagnosis of bvFTD and ALS-bvFTD, which implies high sensitivity of the ALS-FTD-Q. Third, the point prevalence of 7% severe behavioural disturbances in patients with ALS (without a prior diagnosis of bvFTD) in our cohort is in agreement with a pooled prevalence of 8% bvFTD in 570 patients with ALS in a systematic review of population-based or outpatient clinic based studies using family interviews or clinical questionnaires.[5, 6, 18]

The proportion of patients with mild behavioural changes as assessed with the ALS-FTD-Q (11%) is lower than that in other studies (17%–50%).[8, 27, 32, 33] Earlier studies used instruments that have not been validated for the assessment of behavioural changes in ALS and contain items that have not been corrected for motor impairment.[8, 11] In particular, apathy has been shown to be present in up to 50% of patients with ALS.[11, 26, 34] However, apathy was studied with the 14-item FrSBe apathy subscale, of which 7 items are directly related to speaking and moving, which may have led to overestimating motor-related mild behavioural changes, e.g. apathy.[11, 26, 34]

The mild and severe behavioural changes in ALS in the present study have to be interpreted in relation to the cut-offs, which have to be further validated, and in relation to the study population. We did not perform a receiver operating characteristic analysis to define the cut-offs of the ALS-FTD-Q because, for mild behavioural disturbances, a gold standard in ALS does not exist (the FrSBe could not be used for this purpose as it contains motor and speech-related items). For severe behavioural disturbances, we could not use the clinical diagnosis of bvFTD as a gold standard because the bvFTD diagnoses were made before the study (time between bvFTD diagnosis and assessment ranged from 3 to 18 months).

Our study population was largely a prevalence cohort with a relatively long disease duration, and 18% of patients had bulbar-onset ALS (compared with 30% in incidence cohorts).[35] The design of this study with more patients with prevalent than with incident disease was chosen to examine our questionnaire in patients with different disease durations, because previous studies described the development of bvFTD in the course of ALS.[36, 37]

In terms of further validation of the ALS-FTD-Q, the high test-retest correlation should be replicated, and the responsiveness (detection of changes over time)





of the ALSFTD-Q should be explored in depth in a larger sample of patients with incident disease. When sufficient data are collected, a factor analysis may generate insight into subscales and a subset of items that would suffice, which would make the scale even more usable. Compared with a self-report instrument, a potential drawback of the ALS-FTD-Q is that it is limited to patients with a proxy. However, less than 2% of the patients we contacted did not participate because of the absence of a proxy. An important reason to choose an observer-report scale in this study is that frontal lobe dysfunction may interfere with the patient's ability to assess his or her own behaviour. The ALSFTD-Q is a unique and novel instrument to be used in the clinic for the screening of behavioural disturbances in patients with ALS. It is a user-friendly tool with validated clinimetric characteristics.

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## SUPPLEMENTAL MATERIAL

**Amyotrophic Lateral Sclerosis - Frontotemporal Dementia - Questionnaire (ALS-FTD-Q)**

The behaviour of your partner, family member or friend will be evaluated in the following questionnaire. Wherever, "him" or "his" is stated, it can be replaced by "her". Completing the questionnaire should take approximately 10 minutes and ideally should be done in a room separated from the patient. To answer a question, check the box with the most appropriate answer. The questionnaire consists of two parts; A and B.

Date . . - . . - . . . . Filled out by (e.g. partner, sibling, child) . . . . . .
Name of the patient . . . . . .
Date of birth of the patient . . - . . - . . . . Gender of the patient M / F
Highest level of education completed by the patient . . . . . .

**Part A** The following 13 statements compare the ***present*** behaviour of your partner to his behaviour ***three years ago***.

Possible answers are the following:
- completely disagree
- largely disagree
- largely agree
- completely agree

| | | completely disagree | largely disagree | largely agree | completely agree |
|---|---|---|---|---|---|
| 1. | Your partner is less interested in his surroundings | ☐ | ☐ | ☐ | ☐ |
| 2. | Your partner pays less attention to his personal hygiene | ☐ | ☐ | ☐ | ☐ |
| 3. | Your partner puts himself first more often | ☐ | ☐ | ☐ | ☐ |
| 4. | Your partner becomes irritated or angry more easily | ☐ | ☐ | ☐ | ☐ |
| 5. | Your partner's ability to concentrate has decreased | ☐ | ☐ | ☐ | ☐ |
| 6. | Your partner's behaviour is more restless | ☐ | ☐ | ☐ | ☐ |
| 7. | Your partner displays more withdrawn behaviour | ☐ | ☐ | ☐ | ☐ |
| 8. | Your partner seems to undertake more aimless activities | ☐ | ☐ | ☐ | ☐ |
| 9. | Your partner has more problems with memory | ☐ | ☐ | ☐ | ☐ |
| 10. | Your partner contacts strangers more frequently | ☐ | ☐ | ☐ | ☐ |
| 11. | Your partner has an increased urge for sex | ☐ | ☐ | ☐ | ☐ |

(If not applicable; leave unanswered)





Some ALS patients experience compulsive laughter or crying: laughing or crying without a logical reason. The following two statements DO NOT describe this phenomenon; they describe changes in your partner's emotions in general.

| | | completely disagree | largely disagree | largely agree | completely agree |
|---|---|---|---|---|---|
| 12. | Your partner is emotionally less stable | ☐ | ☐ | ☐ | ☐ |
| 13. | Your partner is more often extremely cheerful | ☐ | ☐ | ☐ | ☐ |

**Part B** The following 12 statements are about the behaviour of your partner during the ***past month.*** Please note: some statements describe normal behaviour, while others describe abnormal behaviour. Therefore, please read the statement carefully prior to answering.

Possible answers are the following:
- Never
- Sometimes
- Often
- Always

| | | Never | Sometimes | Often | Always |
|---|---|---|---|---|---|
| 14. | Your partner is suspicious | ☐ | ☐ | ☐ | ☐ |
| 15. | Your partner repeatedly uses the same gestures or sentences | ☐ | ☐ | ☐ | ☐ |
| 16. | Your partner is shameless | ☐ | ☐ | ☐ | ☐ |
| 17. | Your partner is aware of his whereabouts | ☐ | ☐ | ☐ | ☐ |
| 18. | Your partner displays offensive behaviour | ☐ | ☐ | ☐ | ☐ |
| 19. | Your partner is able to assess situations well | ☐ | ☐ | ☐ | ☐ |
| 20. | Your partner hoards food or is preoccupied by food | ☐ | ☐ | ☐ | ☐ |
| 21. | Your partner understands what his disease is about | ☐ | ☐ | ☐ | ☐ |
| 22. | Your partner sees or hears things that are not there | ☐ | ☐ | ☐ | ☐ |
| 23. | Your partner displays childish behaviour | ☐ | ☐ | ☐ | ☐ |
| 24. | Your partner knows which part of the day it is | ☐ | ☐ | ☐ | ☐ |
| 25. | Your partner imitates you or others | ☐ | ☐ | ☐ | ☐ |

**Scoring of the ALS-FTD-Q**
Items 1-13:

| | completely disagree | largely disagree | largely agree | completely agree |
|---|---|---|---|---|
| Value | 1 | 2 | 3 | 4 |

Items 14, 15, 16, 18, 20, 22, 23 and 25:

| | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| Value | 1 | 2 | 3 | 4 |

Items 17, 19, 21 and 24:

| | Never | Sometimes | Often | Always |
|---|---|---|---|---|
| Value | 1 | 2 | 3 | 4 |

**ALS-FTD-Q score:**
item scores are summed to calculate the ALS-FTD-Q score.

**Cut-off values:**
mild behavioural disturbances ≥ 22
severe behavioural disturbances (in the bvFTD range) ≥ 29
These are tentative cut-off values, pending future validation.





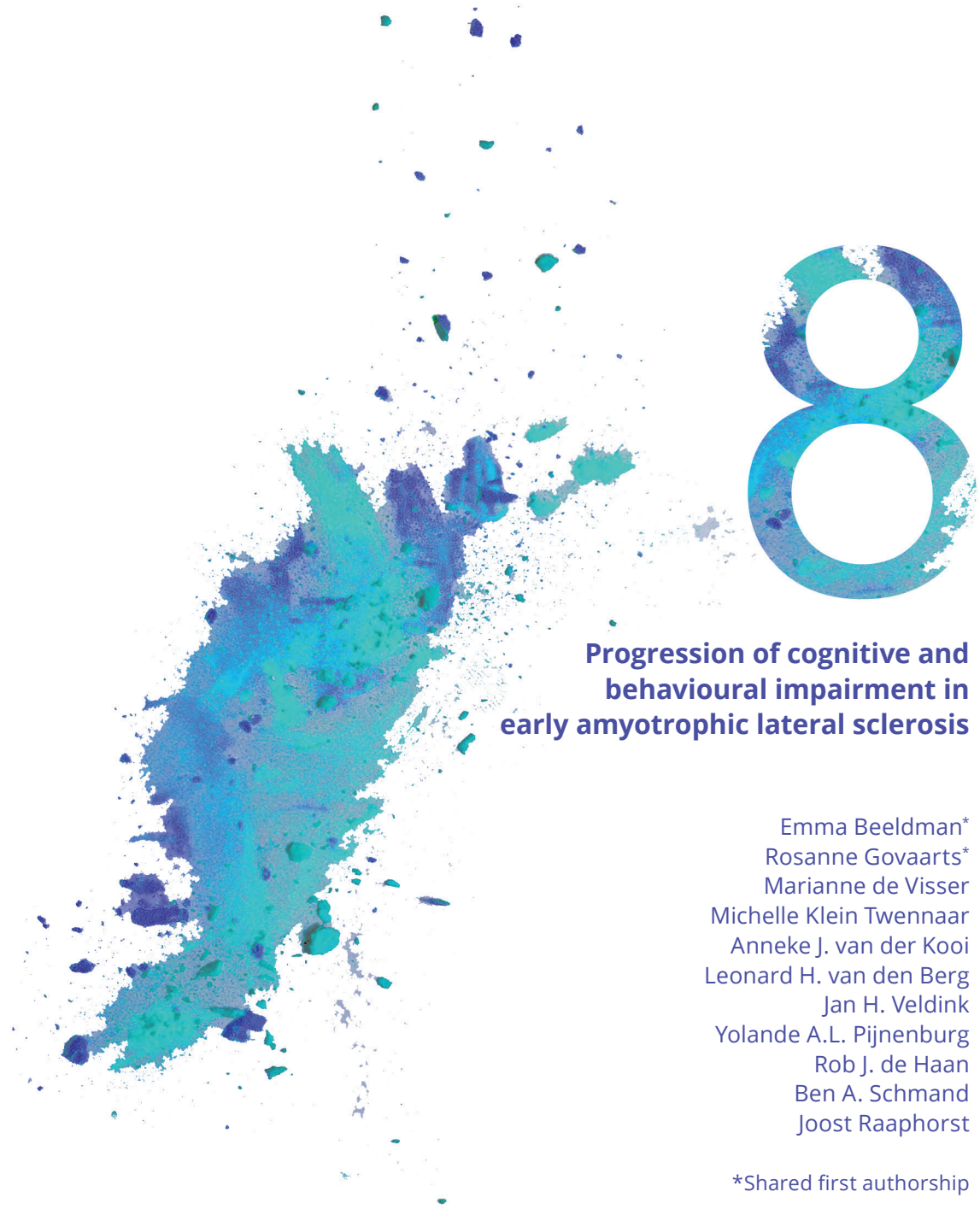
**Appendix e-2:** Face-validity and clinical and demographic characteristics of the test-retest group

Face-validity was examined in a pilot study on 17 ALS patients and their proxies, using a semi-structured interview. The interviewee was asked whether the scale was user-friendly, comprehensible and not too lengthy, if all behavioral problems were covered and if items or their phrasing were felt to be too intimate or offensive. According to these interviews no items were missed or inappropriate.

Test-retest reliability was investigated in the same group of 17 ALS patients including 4 ALS-bvFTD patients: this group consisted of 11 males and 6 females; 14 had limb-onset ALS and three had bulbar-onset ALS. The mean age was 61.7 years (SD 12.1) and the median disease duration was 36 months (range 14-179). The mean ALSFRS-R score was 27.8 (SD 10.4). The mean time between the two assessments was 65 days (SD 26.7). The median ALS-FTD-Q score for these patients at t=0 and t=1 was 8 (range 0-56) and 10 (range 1-68), respectively. The test-retest intraclass correlation of the ALS-FTD-Q total score was 0.89.

# PART 3

## Course and implications of cognitive and behavioural impairment



8

# Progression of cognitive and behavioural impairment in early amyotrophic lateral sclerosis

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## INTRODUCTION

Whether cognitive and behavioural impairment in ALS is progressive is unknown. The majority of longitudinal studies (summarised in supplementary material) are characterised by stable test results, high attrition and underrepresentation of patients with a short disease duration.[1, 2] The aim of this study was to determine progression of cognitive and behavioural impairment in patients with early symptomatic ALS.

## METHODS

At our tertiary ALS clinics, we consecutively recruited patients with ALS with a short disease duration (<12 months). Comprehensive neuropsychological examination and behavioural assessment were conducted at baseline and at 6 months. Patients with behavioural variant frontotemporal dementia (bvFTD) and healthy controls (HC) served as control groups. We used validated tests to correct for motor and speech impairment, for example the verbal fluency index. Inclusion and exclusion criteria and neuropsychological tests, including parallel versions are listed in supplementary material. Test scores were considered abnormal below the 5$^{th}$ percentile, corrected for age and education.[3]

Patient with ALS were classified according to consensus criteria, as having "no", "mild" or "severe" cognitive impairment. "No" is determined by ≤ 1 abnormal neuropsychological test (letter fluency excluded), "mild" by impaired letter fluency *or* impairment on either two (non-overlapping) executive tests *or* two (non-overlapping) language tests (maximum of 3 abnormal tests); "severe" by > 3 abnormal tests (including letter fluency and either two executive or two language tests, as described above).[3]

We used the ALS-FTD-Questionnaire (ALS-FTD-Q) to subdivide patients into groups with "no" (< 22 points), "mild" (≥ 22 and < 29 points) or "severe" (≥ 29) behavioural impairment based on validated cut-off scores.

We further assessed *C9orf72* status, motor function (ALS functional rating scale – revised (ALSFRS-R)), respiratory function (forced vital capacity (FVC)) and anxiety and depression (hospital anxiety and depression scale (HADS)); for detailed descriptions, see supplementary material.

### Statistical analysis

Change scores (follow up minus baseline, raw scores) of neuropsychological tests and the ALS-FTD-Q were examined within groups (Wilcoxon signed rank test) and between groups (Kruskal-Wallis test; or Mann-Whitney U test, where appropriate). Shifts between categories ("no", "mild", "severe") of cognitive and behavioural impairment at baseline and follow-up were recorded for each patient. We compared change scores of the ALSFRS-R, FVC and HADS between patients with ALS with and without category shifts using Kruskal-Wallis test. The occurrence of new impairment on cognitive tests at follow-up was evaluated for individual participants.





## RESULTS

We included 35 patients with ALS with a median disease duration of 8 months (range 4-15) and a mean age of 63.8 years (SD 8.4). Twenty-one patients with bvFTD (including 5 patients with ALS-bvFTD) and 18 HC were included. Groups were matched on age, education and sex (p = 0.4, p = 0.2 and p = 0.3, respectively, supplementary material). At baseline 9 patients with ALS (26%) had mild cognitive and/or behavioural impairment and another 7 (20%) were severely affected. The proportion of patients with bulbar onset or the presence of anxiety or depression symptoms did not differ between these groups (supplementary material).

Follow-up data were obtained at a mean of 6.1 months (SD 0.1) in 28 patients with ALS (80%), 19 patients with bvFTD (91%), and 18 HC (100%). Main reasons for loss-to-follow-up were death, fast disease progression and fatigue.



### Group level

Change scores for letter and category fluency, verbal memory, executive function and social cognition differed between groups, with lower scores in patients with ALS and patients with bvFTD compared to HC (supplementary material). Change scores did not differ between patients with ALS and patients with ALS-bvFTD.

Change scores within groups showed a decline for category fluency in patients with ALS, and for category fluency, social cognition and executive function in patients with bvFTD. HC had higher scores on letter fluency and verbal memory at follow-up.

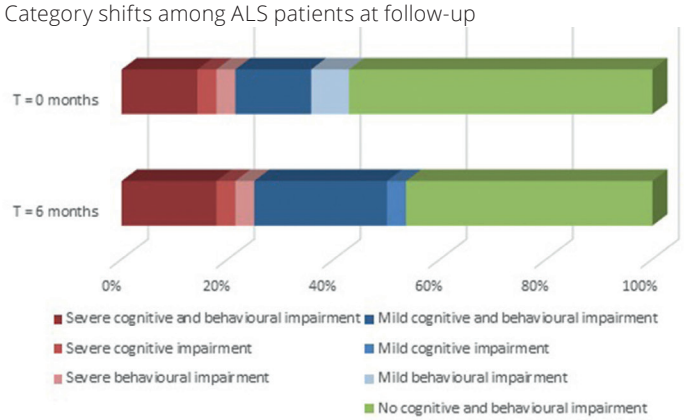
ALS-FTD-Q change scores differed between patients with ALS and HC, but not between bvFTD and HC (supplementary material).

**Individual level - shifts between categories**

Ten out of 28 patients with ALS (36%) shifted towards a more severe category (from "no" to "mild" or "severe" cognitive and/or behavioural impairment), of whom one had a *C9orf72* mutation (figure 1). Fifteen patients with ALS (54%) fell into the same category at baseline and follow-up. Three patients with ALS (11%) shifted from "mild" to "no" cognitive and/or behavioural impairment. Change scores of ALSFRS-R, FVC and HADS did not differ between patients with and without category shifts (supplementary material).

Cognitive impairment at the individual level was also examined by occurrence of new impairment on cognitive tests. Twelve patients with ALS (43%) without cognitive impairment at baseline, had one (n=7) or two (n=5) new abnormal tests at follow-up, mostly category fluency (n=7), anti-saccade test (n=4) and Ekman 60 faces test (n=3). Four patients with ALS with executive dysfunction at baseline showed new impairment at follow-up on tests of executive, memory, language and visuoperceptive functions. The remaining 12 patients, i.e. 7 without and 5 with cognitive impairment at baseline, had no new abnormal tests at follow-up.

**Figure 1.** Category shifts among ALS patients at follow-up




Legend. Proportions of patients with ALS (N=28) with no (green), mild (blue) or severe (red and pink) cognitive and/or behavioural impairment at baseline (upper bar) and follow-up (lower bar). Severe behavioural impairment is compatible with the behavioural variant of frontotemporal dementia. Ten patients shifted towards a more severe category: 6 from "no" to "mild" cognitive impairment, 1 from "no" to "mild" behavioural impairment, 2 from "no" to "severe" behavioural impairment and 1 from "no" to "mild" cognitive impairment and "severe" behavioural impairment.

## DISCUSSION

The findings of a decline of social cognition of patients with ALS and declines of executive and verbal memory functions confirm that cognitive dysfunction is a widespread feature in ALS, even in early disease.[1] It cannot be ascribed to physical, respiratory or affective deterioration, since these were comparable between cognitively stable and progressive patients. Improvement, probably a practice effect, was found in HC on most tests. A lack of practice effects in ALS may be an early sign of frontotemporal dysfunction.

Our study adds to existing literature by showing that in patients with early ALS behavioural decline may occur, compatible with the development of bvFTD.[2] Consequently, our study shows that the frontotemporal syndrome of ALS is not only relevant in the later stages of the disease.

In addition to its strengths (unique cohort, longitudinal design, low attrition), our study has some limitations: groups of patients were relatively small and no disease specific cognitive screening measure was used.

In conclusion, we found progression of cognitive and/or behavioural impairment in more than one third of patients with early ALS. This study may fuel ongoing discussions about the inclusion of cognitive and behavioural symptoms in the diagnostic criteria of ALS.[4, 5]

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## SUPPLEMENTAL MATERIAL

### 1. Overview of longitudinal studies investigating cognitive and/or behavioural impairment in ALS

| Studies examining cognition and behaviour | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Author, year** | **N** | **Follow-up interval (N)** | **Attrition rate** | **Disease duration baseline** | **Type of neuropsychological examination (full or screen) and behavioural screening** | **Cognition at BL Cognition at FU** | **Behaviour at BL Behaviour at FU** |
| Burkhardt, 2017[1] | 40 | 6 mo. (n=24)<br>12-18 mo. (n=10) | 40.0%<br>75.0% | 44.4 mo. | Screen: ECAS, FAB<br>Behaviour: ECAS | BL: 20.8% impaired letter fluency<br>FU: no decline | BL: n/a<br>FU: no decline |
| Floeter, 2017[2] | 15 | 6 mo. (n= n/a)<br>12 mo. (n= n/a)<br>18 mo. (n= n/a) | n/a | 24.4 mo. | Full; domains: executive, language*<br>Behaviour: FBI | BL: n/a<br>FU: decline in letter fluency | BL: n/a<br>FU: no decline |
| Poletti, 2018[3] | 168 | 6 mo. (n=48)<br>12 mo. (n=18)<br>24 mo. (n=5) | 71.4%<br>89.3%<br>97.0% | 19.0 mo. | Screen: ECAS, FAB, MOCA<br>Behaviour: ECAS | BL: ECAS 37% impaired<br>FU: improvement | BL: ECAS 41% impaired<br>FU: no decline |
| Woolley, 2018[4] | 294 | 12 mo. (n=134) | 54.4% | 14.2 mo. | Full; domain executive<br>Screen: ALS-CBS<br>Behaviour: ALS-CBS, FBI-ALS | BL: ALS-CBS 60.7% impaired<br>FU: no decline | BL: ALS-CBS 30.6% impaired<br>FU: ALS-CBS 26.1% impaired. Decline on group level on ALS-CBS and FBI-ALS |
| Xu, 2017[5] | 108 | 6 mo. intervals (n= n/a) | n/a | n/a | Screen: ACE-III, FAB, ECAS<br>Behaviour: MIND-B, ALS-FTD-Q | BL: ACE 30% impaired, FAB 14% impaired. ECAS 22% impaired<br>FU: no decline | BL: ALS-FTD-Q 32.1% impaired, MIND-B 39.4% impaired<br>FU: n/a |

**Table.** Continued.

| Studies examining cognition | | | | | | |
|---|---|---|---|---|---|---|
| **Author, year** | **N** | **Follow-up interval (N)** | **Attrition rate** | **Disease duration baseline** | **Type of neuropsychological examination (full or screen) and behavioural screening** | **Cognition at BL<br>Cognition at FU** |
| Abrahams, 2005[6] | 20 | 6 mo. (n=20) | 0% | 20.6 mo. | Full; domains: executive, language, visuoperception | BL: impairment on fluency<br>FU: decline on 1 language test, improvement on 1 language test and visuoperception |
| Elamin, 2013[7] | 186 | 6 mo. (n=98)<br>12 mo. (n=46)<br>18 mo. (n=11) | 47.3%<br>75.3%<br>94.1% | n/a | Full; domains: executive, memory, language, visuoconstruction | BL: 49.4% impaired<br>FU: decline on visuoconstruction<br>Impaired patients at BL: decline on language, memory and visuoconstruction<br>Non-impaired patients at BL: no decline |
| Gillingham, 2017[8] | 20 | 9 mo. (n=11) | 45.0% | 44.4 mo. | Full; domains executive, visuoperception, language<br>Screen: ALS-Computerized frontal battery; domains social, executive | BL: impairment on executive functions<br>FU: no decline |
| Kasper, 2016[9] | 93 | 3-6 mo. intervals (n = n/a) | n/a | ± 30 mo. | Full; domain: executive* | BL: impairment in 23.7%<br>FU: no decline |
| Kilani, 2004[10] | 18 | 6 mo. (n=14)<br>12 mo. (n=13) | 22.2%<br>27.8% | n/a | Full; domains: executive, language, memory | BL: impairment in executive functions and language<br>FU: no decline |
| Proudfoot, 2015[11] | 61 | 6, 12, 18, 24 mo. (n=29) | 50.8% | 38.6 mo. | Full; domain: executive | BL: impairment on all tests<br>FU: no decline |
| Robinson, 2006[12] | 19 | 6 mo. (n= n/a) | n/a | < 12 mo. | Full; domains: executive, memory, visuoperception | BL: no impairment<br>FU: decline in 36.8% on verbal memory, working memory, visual organization and visuoperception |
| Schreiber, 2005[13] | 52 | 4 mo. (n=32)<br>8 mo. (n=24)<br>12 mo. (n=19) | 38.5%<br>53.8%<br>63.5% | 27.2 mo. | Full; domains: executive, memory, attention | BL: impairment in executive and memory<br>FU: decline in 1 executive test, 1 memory test, 1 attention test<br>Improvement in 1 executive test and 1 memory test |
| Strong, 1999[14] | 13 | 6 mo. (n=8) | 38.5% | 21.1 mo. | Full; domains: executive, memory, visuospatial, language | BL: impairment on visuospatial<br>FU: No decline |

**Table.** Continued.

| Studies examining behaviour | | | | | | |
|---|---|---|---|---|---|---|
| **Author, year** | **N** | **Follow-up interval (N)** | **Attrition rate** | **Disease duration baseline** | **Type of behavioural screening** | **Behaviour at BL<br>Behaviour at FU** |
| De Silva, 2016[15] | 21 | 9-17 mo. (n=5) | 76.2% | 33.4 mo. | Behaviour: FTD-FRS | BL: 47.6%<br>FU: trend of decline |

Legend. Overview of longitudinal studies investigating cognitive and/or behavioural impairment in ALS, arranged by type of examination (respectively cognition and behaviour, cognition only, behaviour only) and first author. BL: baseline measurement; FU: follow-up measurement; mo.: months; y: years; n/a: not available; ECAS: Edinburgh cognitive and behavioural amyotrophic lateral sclerosis (ALS) screen; FAB: frontal assessment battery; MOCA: Montreal cognitive assessment; ALS-CBS: ALS cognitive and behavioural screen; FBI-ALS: frontal behavioural inventory – ALS; FBI: frontal behavioural inventory; ACE-III: Addenbrooke's cognitive examination – III; MIND-B: motor neuron disease behaviour scale; ALS-FTD-Q: ALS – frontotemporal dementia – questionnaire; FTD-FRS: FTD – functional rating scale. *Parallel versions of the neuropsychological tests were used at follow-up.

## 2. Selection procedure and inclusion and exclusion criteria

We prospectively recruited patients with amyotrophic lateral sclerosis (ALS) between September 2013 and December 2016 at tertiary referral centres for ALS in The Netherlands (Amsterdam University Medical Centers and University Medical Centre Utrecht). For comparison, we recruited a group of disease controls, i.e. patients with behavioural variant frontotemporal dementia (bvFTD) or ALS-bvFTD, at a tertiary referral centre for dementia (Amsterdam University Medical Centers). Healthy controls (HC) were recruited through the ALS Foundation Netherlands and participating patients (spouses, family members, friends).

This study was performed in agreement with the Declaration of Helsinki. The local medical ethical committee approved the study. Written informed consent was obtained from all participants at inclusion.

### Inclusion and exclusion criteria

Diagnosis in patients with ALS was probable, probable-laboratory supported or definite ALS, according to the revised El Escorial criteria.[16] Cases could be sporadic or familial (with or without a known mutation). Disease duration had to be less than 12 months in order to fulfil the criterion "early symptomatic ALS" as described previously.[17] Disease onset was defined as the time of the first ALS-related symptom (bulbar dysfunction or limb muscle weakness). All patients had to have an upright forced vital capacity (FVC) > 70%, to avoid overestimation of cognitive deficits due to respiratory muscle impairment.[18] Patients with ALS-bvFTD and bvFTD had possible or probable bvFTD, according to current criteria.[19] They could be sporadic or familial cases and were included irrespective of disease duration. Healthy controls had to have no history of neurological or psychiatric disease. All participants had to be older than 18 years, be fluent in Dutch and have a reliable proxy (partner, relative or close friend), also fluent in Dutch and willing to fill out questionnaires. We excluded participants with other neurological or psychiatric conditions associated with cognitive or behavioural impairment, and participants who used high dose of psychotropic medication or more than 5 alcohol units per day.





## 3. Neuropsychological test battery

| Order | Cognitive test | Cognitive domain | Items (N) | Parallel version |
|---|---|---|---|---|
| 1 | Dutch adult reading test (DART) | Verbal IQ | 50 | No |
| 2 | Benton temporal orientation test (BTOT) | Temporal orientation | 5 | No |
| 3 | Anti-saccade test | Executive functions | 20 | No |
| 4 | Similarities (subtest of WAIS-IV) | Language | 19 | No |
| 5 | Boston naming test (BNT) | Language | 20 | Yes |
| 6 | Judgment of line orientation (JOLO) | Visuospatial functions | 30 | No |
| 7 | Letter fluency index | Executive functions | n/a | Yes |
| 8 | Category fluency (animals, occupation, supermarket) | Executive functions | n/a | No |
| 9 | Visual association test | Visual memory | 12 or 24 | No |
| 10 | Rey auditory verbal learning test (RAVLT) | Verbal memory | 7 | Yes |
| 11 | Letter Number sequencing | Attention | 10 | No |
| 12 | Rivermead behavioral memory test (RBMT) | Verbal memory | 2 | Yes |
| 13 | Ekman 60 faces test | Social cognition | 60 | No |
| 14 | Wisconsin card sorting test (WCST) | Executive functions | n/a | No |

Legend. The neuropsychological test protocol was always performed in this order. Responses to all tests, except the DART, Ekman 60 faces test and WCST, could be performed in writing, when dysarthria was severe. The Ekman 60 faces test and WCST were computerized, but responses could be given orally, when hand function was severely impaired. The letter fluency index was used to correct for speech impairment; it consists of two conditions, the generation condition (the participant is asked to name as many words beginning with a certain letter in one minute, the produced words are written down by the examiner) and the control condition (the participant is asked to read aloud these produced words as quickly as possible). The fluency index is calculated as follows: (time needed for generation - time needed for reading) / total number of items generated. The verbal fluency index reflects the average thinking time per word. For the visual association test, the neuropsychologist chose the appropriate version (short or long version), based on age.

## 4. Measures of motor function, respiratory function, anxiety and depression

The ALS functional rating scale-revised (ALSFRS-R) was administered to patients with ALS (score ranges from 0 to 48; a higher score indicates less impairment).[20] FVC in upright position was assessed in ALS, as a measure of respiratory muscle weakness (percentage of predicted value, corrected for age, sex and height). All participants filled out the hospital anxiety and depression scale (HADS; a higher score indicates more anxiety/depression, with a clinical threshold of 7

on subscales for anxiety and depression. Item 8 "I feel as if I'm slowed down" was removed, to avoid bias due to motor impairment.).[21]

### 5. Participant and disease characteristics at baseline

| | ALS N = 35 | BvFTD N = 21 | HC N = 18 | p-value |
|---|---|---|---|---|
| Age (years) | 63.8 (8.4) | 64.6 (10.2) | 60.9 (10.0) | 0.4 |
| Male (No.,%) | 24 (68.6) | 16 (76.2) | 9 (50.0) | 0.2 |
| Education (years) | 14 (6-18) | 14 (10-18) | 14.5 (10-18) | 0.3 |
| Disease duration (months)[1] | 8 (4-15) | 29 (10-168) | n/a | <0.001 |
| Site of onset (l/b/lb) | 18/15/2 | n/a | n/a | n/a |
| ALSFRS-R score | 42 (31-46) | n/a | n/a | n/a |
| FVC | 94.0 (16.6) | n/a | n/a | n/a |
| Survival (months from symptom onset to death)[2] | 32 (11-73) | n/a | n/a | n/a |
| C9orf72 mutation (No.,%)[3] | 3 (10.3) | 3 (23.1) | n/a | 0.3 |
| HADS anxiety | 4 (0-13) | 5 (0-9) | 3 (0-7) | <0.01 |
| HADS depression | 1 (0-10) | 3 (0-8) | 0 (0-3) | 0.4 |

Legend. Data are expressed as mean (SD) or median (range), where appropriate. ALS: amyotrophic lateral sclerosis; bvFTD: behavioural variant frontotemporal dementia; HC: healthy control; N: number; Site of onset (l/b/lb): limb onset/bulbar onset/limb and bulbar onset; ALSFRS-R: ALS functional rating scale-revised (range 0 to 48, higher score indicates less impairment); FVC: forced vital capacity, percentage of predicted value; n/a: not available; HADS: hospital anxiety and depression scale score, higher scores indicate more symptoms.[1] Disease duration was checked after inclusion and was longer than 12 months in 3 patients (8.6%). [2] By September 26, 2019 (censoring date) 32 patients with ALS (91.4%) and 4 patients with bvFTD (19.1%) had died. [3]*C9orf72* mutation status was missing in 6 patients with ALS and 8 patients with bvFTD.

### 6. Comparison of relevant participant and disease characteristics at baseline between patients with ALS with and without cognitive and/or behavioural impairment at baseline

| | No CI/BI N = 19 | Mild CI/BI N = 9 | Severe CI/BI N = 7 | p-value |
|---|---|---|---|---|
| Site of onset (l/b/lb) | 11/7/1 | 4/4/1 | 3/4/0 | 0.8 |
| C9orf72 mutation (No.,%)[1] | 1 17 | 0 6 | 2 6 | 0.1 |
| HADS anxiety | 4 (0-12) | 3 (1-13) | 5 (2-11) | 0.1 |
| HADS depression | 1 (0-10) | 3 (0-6) | 5 (0-7) | 0.5 |

Legend. Data are expressed as mean (SD) or median (range), when appropriate. CI/BI: cognitive and or behavioural impairment; N: number; Site of onset (l/b/lb): limb onset/bulbar onset/limb and bulbar onset; HADS: hospital anxiety and depression scale score, higher scores indicate more symptoms.[1] *C9orf72* mutation status was missing in 6 patients with ALS.





### 7. Change scores for neuropsychological tests and behavioural assessments at follow-up

| Cognitive test | | ALS N=28 | BvFTD N=19 | HC N=18 | p-value |
|---|---|---|---|---|---|
| Anti-saccade test | | -0.7 (2.9) | -1.1 (2.8) | -0.8 (2.1) | 0.9 |
| WAIS similarities | | 0.8 (3.1) | -0.6 (3.8) | 0.9 (2.6) | 0.4 |
| Boston naming test | | -0.9 (4.9) | -2.2 (5.5) | 0.2 (1.7) | 0.2 |
| Judgement of line orientation | | -0.5 (3.0) | 0.0 (2.5) | -0.5 (2.2) | 0.4 |
| Letter fluency | | -1.8 (5.7)***** | 0.9 (6.0)****** | 9.3 (6.4) | <0.001 |
| Category fluency | Animals | -3.0 (5.5) | -1.5 (2.4) | -1.1 (3.7) | 0.4 |
| | Occupation | -2.6 (3.9)* | -0.5 (2.2) | -0.2 (3.2) | 0.04 |
| | Supermarket | -3.2 (5.4)* | -1.0 (4.0) | 1.4 (5.3) | 0.02 |
| Visual association test | | -0.9 (4.1) | 0.0 (3.6) | -0.5 (5.7) | 0.5 |
| RAVLT | Immediate | -0.1 (7.4) | -1.8 (8.6) | 4.5 (8.0) | 0.2 |
| | Delayed | -0.1 (2.1)* | -0.1 (3.1)** | 2.1 (2.65) | 0.02 |
| Letter number sequencing | | 0.2 (1.9) | -1.4 (3.3) | 0.7 (2.4) | 0.1 |
| RBMT | Immediate | 0.8 (5.0) | -1.0 (4.3) | 1.9 (4.6) | 0.1 |
| | Delayed | 0.4 (5.1) | -1.1 (4.0) | 1.4 (4.2) | 0.3 |
| Ekman 60 faces test | | -0.9 (3.6)* | -4.4 (6.7)** | 2.3 (4.3) | <0.01 |
| WCST | Total errors | 3.0 (15.4) | 15.3 (25.6) | 2.4 (6.9) | 0.1 |
| | Perseverative responses | 0.9 (15.3) | 13.8 (23.6)** | 1.2 (4.2) | 0.04 |
| | Perseverative errors | 1.4 (12.1) | 11.5 (18.7) | 1.0 (2.6) | 0.1 |
| ALS-FTD-Q[#] | | -2.7 (10.3) | -1.4 (7.9) | 2.5 (3.6) | 0.1 |

Legend. ALS: amyotrophic lateral sclerosis; bvFTD: behavioural variant frontotemporal dementia; HC: healthy controls; RAVLT: Rey auditory verbal learning test; RBMT: Rivermead behavioural memory test; WCST: Wisconsin card sorting test; ALS-FTD-Q: ALS-FTD questionnaire. Change scores for all participants with follow up (ALS 28/35, HC 18/18, bvFTD 19/21). Differences between all groups are calculated with the Kruskal-Wallis test, and when significant, with the Mann-Whitney U test for ALS vs. HC (*p < 0.05, *****p < 0.001) and FTD vs. HC (**p < 0.05, ******p <0.001). [#]Change scores of the ALS-FTD-Q did not differ between all groups (ALS, bvFTD and HC); however, when ALS and HC were compared, a p-value of $p = 0.04$ was found.

### 8. Comparison of change scores of motor function, respiratory functions and anxiety and depression between patients with ALS with and without category shifts

Between patients with (n=10) and without (n=18) a shift towards a more severe category of cognitive or behavioural impairment, change scores of ALSFRS-R (-4.0 (range -18.0 – 1.0) vs. -6.5 (range -23.0 – 0.0)), FVC (-11.2 (range -50.2 – 24.7) vs. -16.9 (range -45.8 – 10.0)) and HADS (-2.0 (range -6.0 – 1.0) vs. -0.5 (range -6.0 – 4.0)) did not differ significantly (p = 0.2, 0.4 and 0.4, respectively).

## 9. References


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# 9

## The frontotemporal syndrome of ALS is associated with poor survival

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## ABSTRACT

### Objective
Thirty percent of ALS patients have a frontotemporal syndrome (FS), defined as behavioural changes or cognitive impairment. Despite previous studies, there are no firm conclusions on the effect of the FS on survival and the use of non-invasive ventilation (NIV) in ALS.

### Methods
We examined the effect of the FS on survival and the start and duration of NIV in ALS. Behavioural changes were defined as >22 points on the ALS-Frontotemporal-Dementia-Questionnaire or ≥3 points on ≥2 items of the Neuropsychiatric Inventory. Cognitive impairment was defined as below the fifth percentile on ≥2 tests of executive function, memory or language. Classic ALS was defined as ALS without the frontotemporal syndrome. We performed survival analyses from symptom onset and time from NIV initiation, respectively, to death. The impact of the explanatory variables on survival and NIV initiation were examined using Cox proportional hazards models.

### Results
We included 110 ALS patients (76 men) with a mean age of 62 years. Median survival time was 4.3 years (95% CI 3.53–5.13). Forty-seven patients (43%) had an FS. Factors associated with shorter survival were FS, bulbar onset, older age at onset, short time to diagnosis and a C9orf72 repeat expansion. The adjusted hazard ratio (HR) for the FS was 2.29 (95% CI 1.44–3.65, p<0.001) in a multivariate model. Patients with an FS had a shorter survival after NIV initiation (adjusted HR 2.70, 95% CI 1.04–4.67, p = 0.04).

### Conclusion
In conclusion, there is an association between the frontotemporal syndrome and poor survival in ALS, which remains present after initiation of NIV.






## INTRODUCTION

Thirty to 50 percent of amyotrophic lateral sclerosis (ALS) patients have a frontotemporal syndrome, encompassing behavioural changes and cognitive impairment.[1-5] In 8–10% of ALS patients these changes are more severe and fulfil the criteria for frontotemporal dementia (FTD).[3, 6] The most frequent encountered subtype of FTD is the behavioural variant (bvFTD) albeit language variants of FTD may be found in a minority of ALS patients. Median survival of ALS patients is 3 years after symptom onset and the main cause of death is respiratory failure. The disease course is negatively influenced by older age at onset, early respiratory dysfunction, bulbar onset, a short time to diagnosis and the presence of a C9orf72 repeat expansion.[7-11] Previous studies suggested a negative effect of executive dysfunction or neurobehavioural changes on survival of ALS patients, although the use of general assessment measures for behavioural changes precluded firm conclusions in some of them.[10, 12-15] Indeed, the importance of a valid assessment of the frontotemporal syndrome in ALS, including the use of disease specific measures has been stressed.[1] This would allow for substantiating the presumed association between the frontotemporal syndrome and survival in ALS.[10, 12, 15] The frontotemporal syndrome, in particular the presence of behavioural changes, was found to interfere with the initiation of life-prolonging therapies, i.e. non-invasive ventilation (NIV). An analysis of both cognitive and behavioural changes in patients who used NIV might corroborate this association.[12, 15, 16]

The first aim of this study was to investigate whether a frontotemporal syndrome is an independent risk factor for poor survival in ALS. Secondly, we aimed to gain insight into the effect of the frontotemporal syndrome on NIV initiation and duration in ALS patients.



## METHODS

### Participants
In two of our previous studies, behavioural changes and cognitive impairment were assessed in a total of 110 ALS patients (n=21 and n=89, respectively).[17, 18] ALS patients in both studies were diagnosed with possible, probable or definite ALS according to the El Escorial criteria.[19] Concomitant FTD was diagnosed by the treating neurologist, according to the Neary criteria.[20] Both patient cohorts were recruited from the two tertiary referral clinics for ALS in the Netherlands. Demographic and clinical data were extracted from the databases, i.e. age, years of education, site of onset (bulbar or limb), age at onset, time to diagnosis, disease duration (time between first symptom and study visit), vital capacity

at inclusion (percentage of the predicted value, as measured by handheld spirometry in the upright position), and score on the Hospital Anxiety and Depression scale (HADS; a maximum score of 42 indicates severe anxiety and depression).[21] Physical disability was measured with the amyotrophic lateral sclerosis functioning rating scale - revised (ALSFRS-R; maximum score of 48 indicates no physical disability).[22]

Data on the presence of the C9orf72 repeat expansion was derived from the prospective population based study on motor neuron disease in the Netherlands.[23] DNA was extracted from venous blood using standard protocols.[24] To detect large expanded repeats a repeat primed PCR for the C9orf72 GGGGCC repeat was performed on genomic DNA, as described previously.[24] The C9orf72 repeat expansion was known in 89 (81%) patients in the current study. Time of death was checked in the Municipal Personal Records Database.[25]

**Standard protocol approvals and patient consents**
The medical ethical committees of the hospitals approved the studies. Written informed consent was obtained from all participants at inclusion.

**Assessment of behaviour and cognition**
In the first cohort (n=21), behavioural changes were assessed with the Neuropsychiatric Inventory (NPI).[18, 26] A score of ≥3 points on ≥2 items on the NPI has been used by others as a cut-off for mild behavioural changes in ALS.[17, 27] As described previously by others, we carefully excluded behavioural changes that are more likely due to physical disability (i.e. motor impairment mistaken for apathy) or an appropriate reaction to their diagnosis (e.g. comments about death). Cognitive functions were assessed with a comprehensive neuropsychological examination. Neuropsychological tests were corrected for age, education and dysarthria, as described previously.[18, 28] Cognitive impairment was defined as a score below the fifth percentile on ≥2 tests of executive function, memory or language, according to consensus criteria for cognitive impairment in ALS.[27]

In the second cohort (n=89) behavioural changes were assessed with the ALS-FTD-Questionnaire (ALS-FTD-Q). The ALS-FTD-Q is a proxy-rated, disease-specific, validated instrument to detect behavioural changes in ALS.[17] The items of the questionnaire are based on a systematic review of behavioural changes in motor neuron disease patients with the behavioural variant of FTD. A score of >22 on the ALS-FTD-Q indicates mild behavioural changes. Cognitive functions in the second cohort were assessed with the category fluency test, letter fluency test and the Mini Mental State Examination (MMSE). Cognitive





impairment was defined as ≥2 impaired tests.[27] For the fluency tests we used a cut-off below the fifth percentile of normative scores.[29] For the MMSE, an age and education normative score was used which was adjusted for the highest achievable score of individual patients; some patients could not complete all items due to motor impairment.[30]

**Classification of patients**
Based on consensus criteria for the frontotemporal syndrome in ALS, we defined the following groups: classic ALS, which is not associated with cognitive impairment or behavioural changes, and ALS patients with a frontotemporal syndrome.[27] The frontotemporal syndrome was defined as cognitive impairment, behavioural changes or both. Patients with severe cognitive and behavioural changes who fulfilled the criteria for the behavioural variant of FTD were included in the group "ALS patients with a frontotemporal syndrome".[31]

**Non-invasive ventilation**
There are four Home Mechanical Ventilation centres in the Netherlands from which data were derived on whether the patient started NIV, and the dates on which the NIV was initiated and ended. We also noted whether and when tracheostomal ventilation was initiated.

**Statistical analyses**
Survival was calculated as time from symptom onset to time of death or censoring date (February 24, 2015). As no patients had tracheostomal ventilation, survival following onset of NIV was calculated as time from onset of NIV to time of death or censoring date (July 2014). We used Kaplan-Meier survival analyses and compared the data using the log-rank test. To examine which explanatory variables should be included in the multivariate Cox proportional hazards model, we performed univariate analyses for the following factors: frontotemporal syndrome, bulbar onset, age at onset, time to diagnosis, vital capacity, gender and the presence of the C9orf72 repeat expansion. Explanatory variables with a $p$ value <0.25 in the univariate analyses were included into a multivariate Cox proportional hazards model (using the enter method). Effect sizes were expressed in hazard ratios, statistical uncertainty was expressed in 95% confidence intervals. The defined groups, classic ALS and ALS patients with a frontotemporal syndrome, were compared using independent $t$ test, Pearson Chi-squared test and Fisher's exact test. All tests were two-tailed and statistical significance was set at $p$ <0.05. Statistical analyses were carried out using SPSS version 21 (SPSS Inc., Chicago, IL).

## RESULTS

In total 110 ALS patients were included; 76 men and 34 women; 22 (20%) ALS patients had bulbar onset. The mean age was 62.0 years (SD 11.3; range 34-84). Median time from symptom onset to diagnosis was 10 months (range 2-90). Forty-seven (43%) ALS patients had a frontotemporal syndrome, of whom 8 fulfilled criteria for ALS-bvFTD. Sixteen (15%) patients had only behavioural changes, 18 (16%) had cognitive impairment and 13 (12%) had both. None of the patients had a language variant of FTD. There was no difference in occurrence of the frontotemporal syndrome between the two cohorts ($\chi^2$, $p$=0.99).[17, 18] Demographic and clinical variables for the patient groups are shown in table 1.

### Survival analyses

At the time of analyses, 87 (79.1%) patients had died. The overall median survival time from symptom onset to death was 4.3 years [95% confidence interval (CI) 3.53-5.13]. Table 2 shows univariate analyses of risk factors for survival in all ALS patients. Frontotemporal syndrome, bulbar onset, age at onset, time to diagnosis and the presence of the C9orf72 repeat expansion had $p$ values below 0.25 and were included in the multivariate model.

### Survival of ALS patients with a frontotemporal syndrome

Median survival time was shorter in 47 patients with a frontotemporal syndrome compared to 63 classic ALS patients (3.8 years, 95% CI 2.94-4.73 vs. 5.6 years, 95% CI 3.76-7.41, $p$=0.001). The Kaplan-Meier curve is shown in figure 2A. The impact effect of a frontotemporal syndrome on survival was also observed in a multivariate regression model adjusting for bulbar onset, age at onset, time to diagnosis and the presence of the C9orf72 repeat expansion (adjusted hazard ratio 2.29, 95% CI 1.44-3.65, $p$<0.001; Table 3).

**Figure 1.** Venn diagram of the classification of amyotrophic lateral sclerosis patients (n = 110)

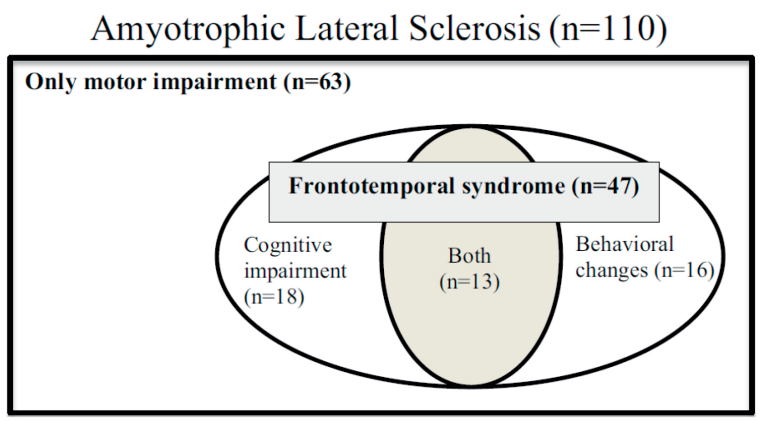







**Table 1.** Demographic and clinical characteristics of ALS patients

| | ALS-classic (n = 63) | ALS-frontotemporal syndrome (n=47) | ALS-frontotemporal syndrome (n=47) | | |
|---|---|---|---|---|---|
| | | | **ALS – cognitive impairment (n = 18)** | **ALS – behavioural changes (n = 16)** | **ALS – both (n=13)** |
| Age at onset, y | 56.5 (12.8) | 61.6 (9.5)* | 60.4 (9.1) | 62.2 (8.9) | 62.4 (11.2) |
| Male sex, n (%) | 39 (61.9) | 37 (78.7) | 13 (72.2) | 14 (87.5) | 10 (76.9) |
| Bulbar onset, n (%) | 6 (9.5) | 16 (34.0)* | 6 (33.3)* | 4 (25.0) | 6 (46.2)* |
| Time to diagnosis, months (range) | 13.6 (1-71) | 14.4 (1-76) | 14.2 (1-36) | 10.9 (1-47) | 19.1 (1-76) |
| ALSFRS-R | 34.2 (8.8) | 31.5 (8.3) | 28.4 (9.4)* | 33.4 (7.1) | 33.4 (7.3) |
| Vital capacity (%) | 84.9 (22.4) | 77.9 (17.1) | 75.8 (21.3) | 82.6 (12.9) | 74.9 (14.8) |
| C9orf72 repeat expansion, n (%) | 2 (3.2) | 4 (8.5) | 1 (5.6) | 2 (12.5) | 1 (7.7) |
| HADS-Anxiety | 10.2 (5.2) | 10.5 (4.7) | 10.9 (4.0) | 9.1 (4.6) | 11.8 (5.5) |
| HADS-Depression | 7.2 (3.7) | 8.2 (3.7) | 7.4 (2.4) | 8.3 (4.1) | 9.4 (4.6) |
| Education, y | 13.9 (2.6) | 14.1 (2.4) | 14.6 (2.2) | 13.3 (2.9) | 14.4 (1.9) |
| NIV initiation, n (%) | 29 (46.0) | 14 (29.8) | 8 (44.4) | 2 (12.5)* | 4 (30.8) |

Legend. Values are mean (SD), unless stated otherwise. All groups are compared to the classic ALS group using an independent $t$ test.
ALS: amyotrophic lateral sclerosis; ALSFRS-R: ALS Functional Rating Scale – Revised (maximum score 48, indicates no disability); HADS: Hospital anxiety and Depression Scale; NIV: non-invasive ventilation; y: years. * $p$ < 0.05

**Table 2.** Univariate analysis of possible risk factors in all ALS patients

| Risk factor | Hazard ratio | 95% CI | p value |
|---|---|---|---|
| Bulbar onset | 2.70 | 1.63-4.49 | <0.001* |
| Age at onset | 1.05 | 1.02-1.07 | <0.001* |
| Time to diagnosis | 0.97 | 0.95-0.99 | 0.001* |
| Vital capacity | 1.00 | 0.99-1.01 | 0.544 |
| Familial/sporadic ALS | 1.25 | 0.64-2.42 | 0.515 |
| Gender | 1.23 | 0.77-1.96 | 0.385 |
| C9orf72 repeat expansion | 1.31 | 1.01-1.07 | 0.040* |
| **Frontotemporal syndrome** | 2.09 | 1.36-3.21 | 0.001* |
| Behavioural changes | 1.95 | 1.08-3.55 | 0.028* |
| Cognitive impairment | 2.01 | 1.15-3.53 | 0.014* |
| Both | 2.28 | 1.19-4.36 | 0.013* |

ALS: amyotrophic lateral sclerosis; CI: confidence interval. * *p* value <0.25; these variables were included into a multivariate Cox proportional hazards model.

### Survival of ALS patients with behavioural changes and/or cognitive impairment

ALS patients with both behavioural changes and cognitive impairment had a median survival time of 3.4 years (n=13; 95% CI 2.14-4.69, *p*=0.01; Figure 2b), compared to 5.6 years in classic ALS. ALS patients with cognitive impairment had a median survival time of 4.3 years (n=18; 4.3 years, 95% CI 2.69-5.81, *p*=0.012; Figure 2b). ALS patients with behavioural changes had a median survival time of 3.8 years (n=16; 95% CI 2.94-4.81, *p*=0.024; Figure 2b). Multivariate analysis for these subgroups was not performed, due to a small size.

### Non-invasive ventilation

Forty-three patients (39%) had used NIV of whom 29 (67%) had classic ALS and 14 (33%) had ALS with a frontotemporal syndrome ($\chi^2$, *p*=0.08). Out of the 43 patients who had used ventilation 8 (19%) had bulbar onset. All except two patients had used NIV until death. Two patients used NIV 2 and 5 days and lived 11 and 18 days, respectively, following the termination of NIV. None of the patients had tracheostomal ventilation.

### Initiation of non-invasive ventilation

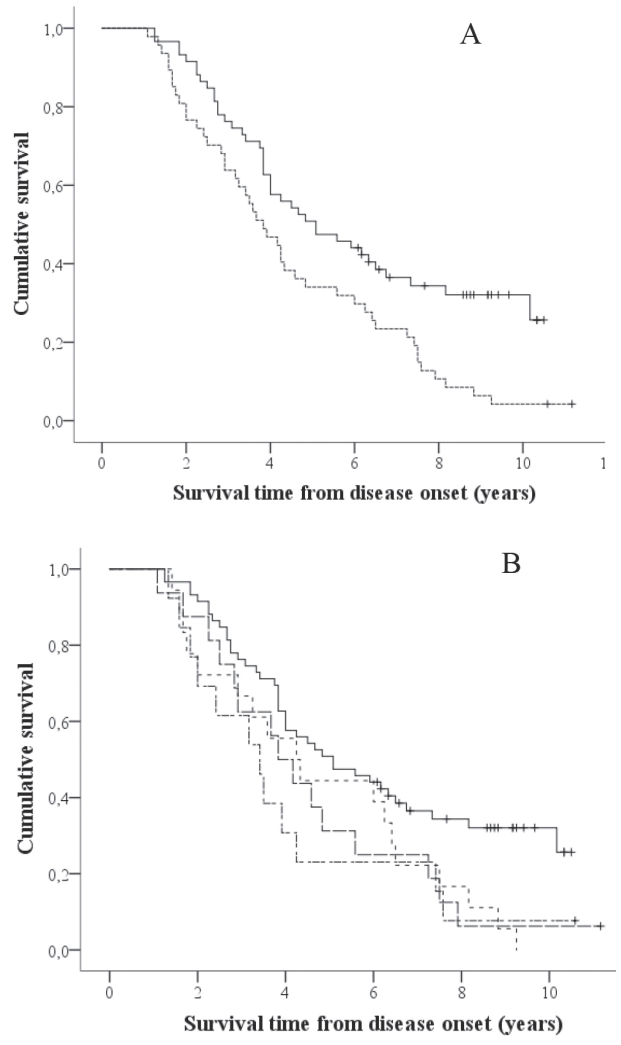
The median disease duration at NIV initiation was 3.9 years (range 0.5-8.2) for classic ALS and 3.1 years (range 1.0-7.0) for ALS patients with a frontotemporal syndrome (*p*>0.05). Patients with behavioural changes initiated NIV less often compared to classic ALS patients (2 out of 16; 12.5% vs. 29 out of 63; 46%, Fisher exact *p*=0.02). The proportion of ALS patients with cognitive changes





(with or without behavioural changes) that initiated NIV did not differ from those with classic ALS.

**Figure 2.** Kaplan-Meier analysis of the effect frontotemporal syndrome on ALS survival



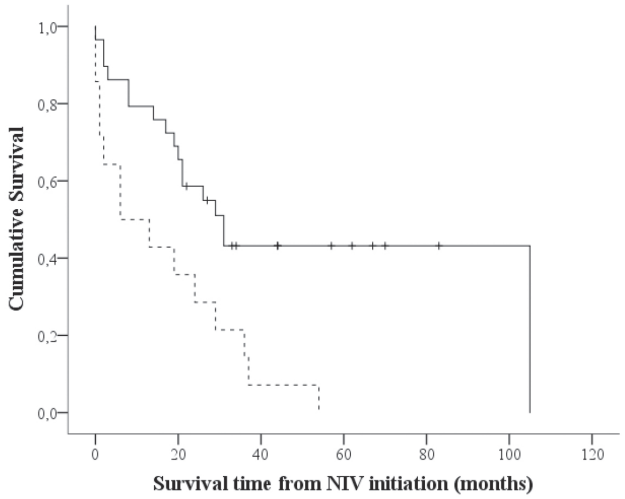

A. Log-rank test for equality of survival functions, *p*=0.005. *Black line* ALS patients without frontotemporal syndrome (n=63); *dotted line* ALS with frontotemporal syndrome (n=47); +: censored cases (n=23). B. Kaplan-Meier analysis of the effect of cognitive impairment and/or behavioural changes on ALS survival. *Black line* classic ALS patients, without frontotemporal syndrome (n = 63); *dotted line* ALS with cognitive impairment (n=18, *p*=0.012); *dashed line* ALS with behavioural changes (n=16, *p*=0.02); *dotted/dashed line* ALS with both cognitive impairment and behavioural changes (n=13, *p*=0.10); +: censored cases (n=23); four patients (two censored) who had a survival time of 15.6-29 years are not displayed in this figure.

**Table 3.** Multivariate analysis for ALS patients with frontotemporal syndrome on survival

| Risk factor | Hazard ratio | 95% CI | p value |
|---|---|---|---|
| Age of onset | 1.04 | 1.02-1.06 | 0.001 |
| Bulbar onset | 1.93 | 1.15-3.24 | 0.013 |
| Extended C9orf72 repeat | 1.54 | 1.17-2.03 | 0.002 |
| Time to diagnosis | 0.96 | 0.93-0.98 | <0.001 |
| Frontotemporal syndrome | 2.29 | 1.44-3.65 | <0.001 |

CI: confidence interval

**Figure 3.** Kaplan-Meier analysis of the effect of the frontotemporal syndrome on ALS survival following initiation of NIV




Log-rank test for equality of survival functions, *p*=0.003. *Black line* ALS patients without frontotemporal syndrome (n=29); *dotted line* ALS with frontotemporal syndrome (n=14); +: censored cases (n=12).

### Survival after non-invasive ventilation

ALS patients who had used NIV had a longer survival than patients without NIV (median 6.0 years, 95% CI 4.4-7.6 vs. 3.8 years 95% CI 3.2-4.3, *p*=0.03). ALS patients with a frontotemporal syndrome had a shorter survival after NIV initiation compared to those with classic ALS (median 6 months, 95% CI 0.0-18.9 vs. 31 months 95% CI 19.9-43.0, *p*=0.009; Figure 3). The impact effect of a frontotemporal syndrome on survival (following NIV) was also observed in a multivariate regression model adjusting for site of onset, age at onset, time to diagnosis and the presence of the C9orf72 repeat expansion (HR 2.7, 95% CI 1.2-6.0, *p*=0.02).





In an exploratory analysis, we analysed the effect of the frontotemporal syndrome on survival in the non-ventilated group. Non-ventilated ALS patients with a frontotemporal syndrome showed a trend to a shorter survival compared to classic ALS patients without NIV (median 4.00 years, 95% CI 3.43-3.82 vs. 3.59 years 95% CI 2.55-4.62, *p*=0.06)

## DISCUSSION

In 110 patients with ALS we examined the effect of the presence of the frontotemporal syndrome on survival and NIV initiation and duration. We showed that the concomitant presence of the frontotemporal syndrome (behavioural changes, cognitive impairment or both) in patients with ALS is associated with a significantly shorter survival independent of other prognostic factors. We also found that the survival after NIV initiation was significantly shorter in ALS patients with a frontotemporal syndrome compared to classic ALS. Thus, our findings suggest an association between the frontotemporal syndrome and poor survival in ALS patients, which remains present following the initiation of NIV.

Known factors for a poor prognosis are older age at onset, early respiratory dysfunction, bulbar onset, short time to diagnosis and the presence of the C9orf72 repeat expansion.[7-11] Early respiratory dysfunction was not a relevant prognostic factor in our study, possibly because the median vital capacity (percentage of predicted value) of our patients was 84% at inclusion.[18]

Our study strengthens and extends findings from previous studies as our data robustly showed that not only cognitive changes, but also behavioural changes negatively affect survival in ALS.[10, 12, 13, 15] Importantly, for the assessment of behavioural changes we used a disease specific instrument which has shown to prevent overestimation of behavioural changes in ALS.[17]

NIV is a life-prolonging therapy in ALS and, therefore, an important variable to consider in survival studies in ALS.[32] Reports on analyses on NIV use provide clues on possible causes of reduced survival in ALS patients with a frontotemporal syndrome.[10, 15] We showed that in particular ALS patients with behavioural changes (and not cognitive changes) less often initiated NIV, and that ALS patients with a frontotemporal syndrome had a shorter survival after NIV initiation compared to classic ALS patients. Our data, due to relatively low numbers, do not enable us to differentiate whether apathy, disinhibition or dysexecutive behaviour mediates this difference. An association between frontotemporal dysfunction and either the initiation of NIV, or survival following

NIV, has been shown by others.[12, 15] Our study extends these findings and suggests that a shorter survival due to a frontotemporal syndrome can be explained by both a lower proportion of ALS patients (with a frontotemporal syndrome) initiating NIV, and a shorter survival of ALS patients with a frontotemporal syndrome, following NIV.[12, 15] Larger cohorts are needed to confirm this association and other issues. In particular, more data should be obtained on compliance with NIV, the role of patients, proxies and physicians in the decision-making process, and on end of life practices in ALS patients with the frontotemporal syndrome.[33-35] In addition, a study in a larger cohort may elucidate the impact of different aspects of behavioural changes in ALS (i.e., apathetic vs disinhibited type).[36]

In addition to the strengths of our study, some limitations need to be addressed. The assessment of behavioural changes and cognitive impairment differed slightly between the two cohorts. However, no differences in outcomes were shown between the cohorts. We included more prevalent than incident patients, i.e. the disease duration was more than one year in most patients. This is reflected by a relatively long survival of the cohort, probably due to a lower proportion of patients with a rapid disease course. The cognitive testing in one cohort focused on executive functions, which may have resulted in an underestimation of cognitive deficits, because other cognitive domains can be affected in ALS, even in the absence of executive deficits. As fluency is an important aspect of executive functioning, the association of cognitive dysfunction with survival in our study may have in part been driven by executive dysfunction, thus corroborating previous findings from Elamin et al.[10, 37-39] Due to small numbers we were not able to perform multivariate analysis in the subgroups (i.e. patients with only cognitive impairment, patient with only behavioural changes, and patients with both). Finally, we were unable to retrieve sufficient data on the initiation and duration of feeding by gastrostomy.

In conclusion, we have shown an effect of the frontotemporal syndrome on survival in ALS, which is in part related to a shorter NIV use as compared to classic ALS patients. These findings underline the importance of the assessment of cognitive impairment and behavioural changes in ALS patients and contribute to a better understanding of prognostic factors in ALS.





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# 10

## General discussion

In this thesis we aimed to investigate the profile and course of (mild) cognitive and behavioural impairment in amyotrophic lateral sclerosis (ALS). Furthermore, we developed easy-to-use tools for the detection of cognitive and behavioural impairment in ALS patients in daily clinical practice.

**Part 1. Cognitive and behavioural impairment in ALS and behavioural variant FTD**

In 2010 we investigated the cognitive profile of ALS by means of a meta-analysis.[1] At that time, sixteen neuropsychological studies in ALS patients were eligible for inclusion, which resulted in effect sizes with wide confidence intervals for multiple cognitive domains. Since 2010, the interest in cognitive impairment in ALS has grown, which led to the publication of many neuropsychological studies in ALS. We therefore updated the meta-analysis (**chapter 2**) in order to more precisely determine the cognitive profile of ALS. The main finding of our meta-analysis was the extent of impairment of social cognition in ALS patients, compared to healthy controls. Social cognition is a complex cognitive domain which encompasses both theory of mind (ToM) and emotion recognition. Studies in bvFTD have shown important deficits of social cognition, which may be the hallmark of frontal degeneration.[2, 3] Decline in social cognition has even been shown in presymptomatic FTD mutation carriers, approximately 6 years before symptom onset.[4] In ALS, social cognition has only recently been recognized and our meta-analysis included 6 studies that investigated social cognition, of which 5 investigated either ToM or emotion recognition. Only recently, it is considered a key element of the cognitive profile and is as such included in the criteria for cognitive impairment in ALS.[5] The impact of social cognition deficits in ALS patients may not be fully elucidated; the literature on bvFTD reveals that the loss of empathy in bvFTD patients does not only result in an increased caregiver burden, but can also lead to marital problems.[6, 7] Therefore, in bvFTD, studies are currently focussing on therapies to improve social cognition, both pharmacologically and with psychosocial interventions.[8-10] In light of these findings studies on the impact of social cognition deficits both in the ALS patient and their caregiver are needed. When deficits in social cognition are suspected it can be advised to offer more psychological support to the caregiver.

Another important finding of our meta-analysis was the important role of verbal memory in the cognitive profile of ALS. Over the years there has been much debate about the presence of memory deficits in ALS. The main issue with the assessment of (verbal) memory is that it also requires other cognitive functions, such as executive functions.[11, 12] It has been suggested previously that memory impairment in ALS cannot be fully explained by the presence of executive dysfunction.[13] In the current criteria for cognitive impairment in ALS the





presence of isolated memory deficits is not sufficient for a diagnosis of cognitive impairment in ALS (ALS-CI).[5] In the Edinburgh Cognitive and Behavioural ALS Screen (ECAS), memory tests are included in the ALS non-specific part of the screen.[14] However, imaging studies performed by our research group and others have shown evidence of hippocampal volume loss in ALS patients with verbal memory deficits (immediate and delayed story recall).[15, 16] Evidence of functional connectivity changes and degeneration in the hippocampus and Papez circuit in ALS has also been found by others.[17-19]

It remains unclear whether this evidence should give memory impairment a more important role in the ALS clinic, i.e. should we specifically ask about memory deficits when we suspect cognitive impairment? When we examined the literature on behavioural changes in MND-FTD patients (**chapter 4**) we found that the most frequently reported symptom was memory impairment, albeit not a behavioural symptom. The lay term 'memory impairment' might be used to describe cognitive decline in general. In our study examining the validity of the ALS-FTD-Q (**chapter 7**) we found that the item 'your partner has more problems with memory' had a good item – total score correlation, indicating that it attributes equally to the scale as the behavioural items. The same applies to three other items investigating attention and orientation. It might therefore be wise to ask the proxy about memory impairment in the outpatient clinic, as it might provide an easy insight in the presence of cognitive impairment, the precise nature of which could be examined in more detail, if needed.

***Cognitive impairment in bvFTD***

Cognitive impairment in bvFTD is often overshadowed by the presence of severe behavioural impairment and is not a prerequisite for a diagnosis of bvFTD.[20] The bvFTD criteria specify the existence of impairment in executive functioning, with relative sparing of episodic memory and visuospatial functions. Other cognitive domains, such as social cognition, language and attention are not mentioned. The complete cognitive profile of bvFTD has never been systematically examined and the "cognitive" overlap with ALS is not known. In **chapter 3** we therefore performed a systematic review and meta-analysis of the literature on cognitive impairment in bvFTD and compared this with our meta-analysis of the cognitive profile of ALS. We showed that the cognitive profile of bvFTD consists of deficits in social cognition, verbal memory, fluency and other executive functions. There was a considerable overlap between the cognitive profiles of bvFTD and ALS, indicated by a high correlation coefficient of the ALS-specific cognitive domains. We excluded the domain language from this analysis, because language showed a relatively higher effect size in ALS patients than in bvFTD patients. This difference is probably related to the exclusion of

patients with language variants of FTD in the bvFTD meta-analysis, as opposed to the ALS meta-analysis.

The important role of verbal memory impairment in bvFTD was somewhat surprising, as the current diagnostic criteria report a relative sparing of episodic memory.[20] In our study we were not able to examine the complex interplay between executive functions and memory deficits. Even though the effect size of executive functions was smaller than the effect size of verbal memory, this does not rule out an interaction between the two domains. As described previously, evidence of hippocampal involvement in ALS has been shown.[15, 17, 18] Imaging studies in bvFTD have also shown a lower metabolism in the anterior parahippocampal and inferior temporal gyri in bvFTD patients, as well as atrophy of multiple brain regions including the right anterior hippocampus, anterior cingulate cortex and left paracingulate gyrus.[21-23] Therefore, it has been proposed that both an amnesic variant and non-amnesic variant of bvFTD exist.[24]

***Behavioural impairment in ALS***

Behavioural impairment, which is the hallmark of bvFTD, also plays a significant role in ALS, as it negatively influences caregiver burden and caregiver's quality of life.[25-27] It has been assumed that the behavioural changes in ALS patients are consistent with those found in bvFTD, although this has never been systematically examined. It is clinically relevant to gather evidence of the overlap of behavioural symptoms between both diseases, as behavioural questionnaires developed for FTD are also being used in the ALS population. The application of FTD questionnaires in the ALS population poses another problem, namely the bias that occurs due to motor and speech impairment. For example, a question such as 'the patient moves around less' which aims to examine the presence of apathy might be falsely positive in an ALS patient who has lost the ability to walk. In **chapter 4**, we therefore aimed to determine the most frequent behavioural changes in ALS, in order to develop a new behavioural questionnaire for ALS patients (**chapter 7**). We systematically reviewed the literature on behavioural changes in motor neuron disease - FTD patients (MND-FTD), which consisted mostly of small case series and case reports. We also included patients with progressive muscular atrophy and primary lateral sclerosis in the study, because cognitive and behavioural impairment has also been found in these disease variants.[28, 29] The inclusion of patients with other MND variants may have increased the heterogeneity in our study, although the vast majority of included patients was diagnosed with ALS.





When looking specifically at ALS, we found nine cohort studies reporting on the frequency of ALS-FTD, which was approximately 8%. The frequency of mild to moderate behavioural impairment had a wide range from 17% to 88% due to the variation in methodology. In these studies, behavioural changes were evaluated in an interview with the proxy or with a behavioural questionnaire. These questionnaires were not specifically designed to measure behavioural impairment in ALS patients. Since 2011, multiple behavioural questionnaires, specifically designed for ALS patients, have been developed and many studies have used these screening tools. This has allowed for a better estimate of the frequency of behavioural changes, i.e. 13% to 48%.[14, 30-36] However, the frequency estimate still has a broad range, which is probably, at least partially related to heterogeneity among studies, i.e. diverging disease duration and physical impairment.

Our systematic review on behavioural changes in MND-FTD patients showed that the most frequently reported behavioural changes include perseveration, apathy, disinhibition, loss of disease insight and indifference. Memory complaints were also frequently reported, but are not considered a behavioural symptom. One of the limitations of this study is that the results cannot be directly compared to bvFTD patients, and therefore, it is not clear whether the behavioural profiles of these two diseases are similar. To the best of our knowledge, there have only been two studies comparing the behavioural symptoms of ALS-bvFTD patients and bvFTD patients. Both studies found a different behavioural profile in bvFTD as compared to ALS-bvFTD patients, with more social disinhibition, dietary changes (binge eating and altered food preferences), inertia and complex repetitive behaviours in bvFTD patients.[37, 38] However, the largest study (56 ALS-FTD patients and 185 bvFTD patients) had a retrospective study design which relied on information from clinical records, which might have resulted in reporting bias.[37] The other study included small groups of 23 bvFTD patients and 20 ALS-FTD patients.[38] When comparing the most frequently reported symptoms in our systematic review to the current diagnostic criteria for bvFTD they show great resemblance.[20] The only exception being the prominent role of hyperorality and dietary changes in the criteria, which occurred only in 4.1% of the patients in our review. Future studies should prospectively investigate behavioural symptoms in a large group of ALS, ALS-bvFTD and bvFTD patients in order to determine the behavioural profile of all three diseases. It is not only important to determine the overlap, but also to investigate the differences between ALS and FTD. Specific behavioural symptomatology could provide insight into the involvement of different brain regions in these three diseases. Together with imaging and pathological studies in these patient groups, this could contribute to a clearer understanding of the pathophysiology underlying both diseases.

**Part 2. Screening for cognitive and behavioural impairment**

Given the above, it is crucial to define the complete clinical picture in every ALS patient. The gold standard to diagnose cognitive impairment is an extensive neuropsychological examination (NPE), but tests need to be adjusted for motor and speech impairment when used in ALS patients. An NPE might not be available in every ALS clinic and is also time-consuming. Behavioural changes are typically examined with a thorough interview with the patients' caregiver, but such an interview is quite long and there might not be enough time during a full consultation schedule at the outpatient clinic. Therefore, short screening tools, which exclude bias due to motor or speech impairment and are easy to administer and widely applicable, could be beneficial to obtain a quick insight into the presence of cognitive and behavioural impairment.[39]

There are some issues as regards assessment of cognitive impairment in ALS patients. An NPE requires intact dexterity and speech, as many neuropsychological tests are time-dependent, which is clearly an issue in ALS patients. We showed that a frequently used screening tool for frontal dysfunction, the Frontal Assessment Battery (FAB), cannot be completed by approximately 20% of ALS patients. Also, a correlation between the FAB and the ALS functional rating scale – revised, i.e. a measure of physical and respiratory disability, was found, indicating that at least part of the FAB score is related to physical impairment.[40] These results indicate the need for adapted neuropsychological tests for ALS patients that do not require intact dexterity or speech.

One of the most frequently used, and frequently impaired tests in ALS is the verbal fluency test. The patient is asked to name as many words starting with the same letter in one minute. One can imagine that slurred speech results in a reduced number of words per minute. An alternative is the written verbal fluency, however normative data of this test is not available. Therefore, the verbal fluency index was developed, in which the thinking time per word is calculated ((60 seconds – time to read the words aloud) / number of produced words). In **chapter 5** we provided normative data for the Dutch verbal fluency index based on a cohort of 273 healthy volunteers. In this study the fluency index was calculated for verbal fluency with the letter 'D'. This letter is comparable in terms of difficulty to the letters 'F' and 'S' in English. One of the limitations of this study is that it does not provide normative data for other fluency tests, such as category fluency, which is also a frequently used test in ALS. Both tests rely on frontal and temporal lobe functions, but the letter fluency test depends more on frontal lobe function, whereas retrieval in the category fluency test is more associated with the temporal lobe.[41, 42] It has also been suggested that letter fluency is associated with educational level, whereas





category fluency is associated with age.[43] Therefore, our normative data for the letter fluency test cannot be directly translated to the category fluency test and normative data for the category fluency index should be investigated separately.

***Screening for cognitive impairment in ALS***

The development of normative data for adjusted neuropsychological tests facilitates the examination of cognitive impairment in ALS patients. This is needed as the current consensus criteria for frontotemporal dysfunction in ALS recommend screening for cognitive impairment in every ALS patient.[5] When cognitive impairment is suspected based on the screening results, a complete neuropsychological examination is advised.

At the start of this thesis screening instruments specifically designed for cognitive impairment in ALS were lacking. The available screening instruments were either too general (e.g. Mini Mental State Examination, Montreal Cognitive Assessment) or did not adjust for impaired dexterity and speech (FAB, Addenbrooke's cognitive examination revised). Therefore, in **chapter 6** we described the development and clinimetric properties of a new screening tool, the ALS-FTD-Cognitive screen. The cognitive domains covered in our new screen, i.e. social cognition, letter fluency, verbal memory and language were chosen based on the cognitive profile of ALS, described in **chapter 2**. We included neuropsychological tests that did not rely on dexterity and speech, with available normative data. The ECAS was published during our study and is currently the most frequently used screen in ALS.[14] We therefore compared both screening tools with a complete neuropsychological examination in a subset of our study population. We found moderate clinimetric properties of the ALS-FTD-Cog, i.e. a sensitivity and specificity of 65% and 63.5%, respectively. The sensitivity and specificity of the ECAS, measured in a smaller group of patients, were good (83.3% and 91.3%, respectively).

One of the possible explanations for the disappointing clinimetric properties of the ALS-FTD-Cog might be the inclusion of the 'faux pas test' as a measure of social cognition. The task consists of multiple short stories, half of which contain a faux pas. The examinee is asked whether a faux pas was present and if so, how the person who was offended would feel. When administering the screen, we noticed difficulties, both in patients and healthy controls to understand the instructions. Especially attributing an emotion to the situation at hand proved cumbersome and many test subjects named multiple emotions. Unfortunately, there is no literature about this type of difficulties of the faux pas test and the observation in our cohort is therefore not supported by evidence. In addition, there are other studies that suggest the faux pas test might have less

discriminative potential between FTD and other neurodegenerative diseases, although this is contradicted by others.[2, 44, 45]

Due to moderate clinimetric properties of the ALS-FTD-Cog, we do not recommend its use in ALS patients. The sensitivity and specificity of the ALS-FTD-Cog in our group of bvFTD patients were very high (94.4% and 100%, respectively), which could indicate that it can be used in this patient category to identify cognitive impairment. However, cognitive screens are most informative at the moment of diagnosis, whereas our bvFTD patients were mostly prevalent cases, reflected by a disease duration ranging from 9 to 166 months. Consequently, most patients had an advanced disease stage and severe cognitive impairment, which was corroborated by the NPE. We do not expect preserved clinimetric properties in bvFTD patients with less advanced disease, as we have shown only moderate sensitivity and specificity in our cognitively less impaired ALS patients.

***Other cognitive screening tools for ALS patients***

Currently there are other cognitive screening tools available for use in ALS patients, namely the ALS-Brief Cognitive Assessment (ALS-BCA), the ALS Cognitive Behavioral Screen (ALS-CBS), the Penn State Screening examination of Frontal and Temporal dysfunction Syndromes (PSSFTS) and the University of California San Francisco – Screening Battery (UCSF-SB).[46] We recommend to compare these screening tools in a large cohort study, in order to select the screen with the best clinimetric properties.

***Screening for behavioural impairment in ALS***

In **chapter 7** we described the development and validation of the amyotrophic lateral sclerosis – frontotemporal dementia – questionnaire (ALS-FTD-Q). The selection of items for the questionnaire was based on our systematic review of behavioural changes presented in **chapter 4**. We included the most frequently reported behavioural symptoms in the questionnaire and examined the questionnaire in two ways. First, a pilot study was conducted to examine face-validity, in which 17 proxies of ALS patients filled out the ALS-FTD-Q. Afterwards a semi-structured interview was performed to determine whether the scale was user-friendly and to investigate if any behavioural symptoms were missing. The interviews revealed no difficulties with filling out the questionnaire and no missing behavioural changes. Second, a validation study was performed in a cohort of patients with ALS (n=103), patients with ALS-bvFTD (n=10), patients with bvFTD (n=25), patients with other neuromuscular diseases (n=39, without a known association with behavioural impairment) and disease controls (n=31) who were evaluated at the neurology outpatient clinic for other complaints (for example tremor or headache). The inclusion of patients with other





neuromuscular diseases allowed to account for the possible effect of chronic illness and motor disabilities on behaviour.

The clinimetric evaluation of the ALS-FTD-Q showed substantial internal consistency and a good item-total score correlation for most items. The items hypersexuality and euphoria had a lower correlation. These behavioural changes occur less frequently than most other items in the questionnaire (8.2% and 7.1%, respectively). The item hypersexuality was not always filled out, primarily because in some cases the proxy was a child or close friend of the patient. There also might be a taboo against talking about sexuality, especially in the older population. The second item, euphoria, might have been difficult to distinguish from compulsive laughter, which occurs as a pseudobulbar symptom in ALS. The construct validity, examined by correlating the ALS-FTD-Q with measures that investigate similar and different constructs was good. The inclusion of a healthy control group allowed us to establish a lower limit cut-off. A cut-off for severe behavioural changes was chosen based on the available data of ALS-bvFTD and bvFTD patients. The distinction between mild and severe behavioural changes is clinically important and allows to assess significant progression over time. This distinction is lacking in another frequently used ALS behavioural questionnaire, the Motor Neuron Disease Behaviour Scale (MiND-B), but is included in the Beaumont behavioural inventory (BBI) and the ALS cognitive behavioral screen (ALS-CBS).[30-32]

A recent review of all available cognitive and behavioural screens for ALS showed comparable results for the ALS-FTD-Q, BBI and ALS-CBS, all three of which cover all relevant behavioural domains.[46] One study directly compared the BBI to the ALS-FTD-Q showing an overall high correlation. However, the authors concluded that some behavioural aspects are not extensively measured by the ALS-FTD-Q, i.e. apathy, increased sensitivity to sensory stimuli and grammatical mistakes, and that the BBI might be more sensitive to detect these changes.[47] The BBI consists of 41 items compared to 25 items of the ALS-FTD-Q, and it is therefore not surprising that this allows for detection of more (subtle) changes. The aim of the development of the ALS-FTD-Q was to provide a quick screening tool for the most frequent behavioural changes, which could never replace a thorough interview with the patient's caregiver. It should be used in the outpatient clinic to screen for mild behavioural changes, as these often go undetected during the consultation.

Since the publication of the ALS-FTD-Q it has been translated in seven languages, including French, German and Japanese. A cross-cultural validation study of the Japanese version has been performed, which showed similar clinimetric properties.[48]

**Part 3. Course and implications of cognitive and behavioural impairment**

The clinical overlap between ALS and FTD supports the existence of a disease spectrum with pure ALS and pure FTD on both ends. It is therefore logical to assume that mild cognitive and behavioural impairment in ALS is a precursor of full-blown FTD. However, there are only a few longitudinal cognitive and behavioural studies in ALS which show diverging results. Some studies found stable or even improved cognitive and/or behavioural test results at follow-up, whereas other studies did find some progression.[33, 36, 49-52] Most of these studies included 'prevalent' ALS patients, i.e. patients with diverging disease duration.[50, 53-55] ALS with a protracted disease course may well be a different variant in the MND spectrum than rapidly progressive ALS. When examining mostly patients with a protracted course this could introduce bias. To avoid bias, 'incident' ALS patients, i.e. patients with a disease duration of less than 12 months should be included. Confusingly, the term 'incident' is sometimes defined as less than twelve months from diagnosis. We consider the latter definition to be less accurate, as it is well known that a short diagnostic delay is associated with reduced survival.[56]

In **chapter 8** we described the results of a longitudinal cohort study of 'incident' ALS patients. We included 35 ALS patients with a median disease duration of eight months, 21 bvFTD patients and 18 healthy controls. At baseline 26% of ALS patients had mild cognitive and/or behavioural impairment and 20% had severe impairment. At follow-up six months later ten patients (36%) showed progression of cognitive and/or behavioural impairment. Even though our study sample was small, most of the 'progressors' (n=6, 60%) had developed mild impairment after 6 months. Three patients were impaired in one of the two categories (cognitive or behavioural impairment) at baseline and had developed impairment in the other category at follow-up. With this study we have shown that cognitive and behavioural impairment can not only develop, but also progress during the disease course. Even though we achieved a low attrition rate (20%), longitudinal studies in incident ALS patients can be challenging due to the fast progression of motor symptoms. When examining progression in a cohort of prevalent patients it should be noted that the follow-up period needs to be extended significantly. With a follow-up period of 6 to 12 months it is not surprising that most studies have failed to show progression of cognitive and behavioural symptoms over time. However, extending the follow-up period is complicated as performance on neuropsychological tests can be influenced by hypercapnia (caused by respiratory dysfunction) and the examination of patients in more advanced disease stages is burdensome.





***Non-invasive ventilation and survival in ALS patients with cognitive and behavioural impairment***

The presence of cognitive and behavioural impairment will likely influence decisions about life-prolonging therapies and advance care planning. Especially in the case of progression of cognitive and behavioural impairment and the development of bvFTD it might no longer be possible to make shared medical or legal decisions.[57-59] Furthermore, it has been shown that life-prolonging therapies, such as non-invasive ventilation (NIV) are less often initiated in ALS patients with cognitive and behavioural impairment.[60] Whether this contributes to a reduced survival in this patient group was as yet unknown. Therefore, in **chapter 9** we examined the use of NIV in a cohort of prevalent ALS patients with and without cognitive and behavioural impairment and investigated the effect on survival. We found that survival is reduced in patients with cognitive and/or behavioural impairment (3.4 years vs. 5.6 years). However, the survival of patients without cognitive and behavioural impairment was longer than the median survival reported in the literature, which is most likely a reflection of the inclusion of prevalent patients. We also found that patients with behavioural impairment less often initiated NIV. Surprisingly, this was not seen in patients with cognitive or both cognitive and behavioural impairment. Our retrospective study design did not allow to evaluate whether the reduced initiation of NIV was the result of a decision made by the patient, caregiver, physician or any combination of the three.

It has been previously suggested that patients with cognitive and behavioural impairment have more difficulty with compliance to therapy, i.e. the correct use of the machine and use during the prescribed hours.[61-63] In our study we showed that patients with cognitive and behavioural impairment had a reduced survival after the initiation of NIV compared to patients without cognitive and behavioural impairment (6 months vs. 31 months). Only two patients discontinued NIV within one week after initiation and all other patients used NIV until death. However, data on the compliance with NIV were not available. The significantly shorter survival after the start of NIV does suggest that ALS with cognitive and behavioural impairment has a more aggressive course. When looking at the ALS-FTD disease spectrum, it is known that survival in ALS is much shorter than in FTD (3 vs. 8 years).[64, 65] It has also been shown that patients with ALS-FTD who present with signs of FTD have a longer survival than those who present with motor impairment.[65] This suggests that the involvement of motor neurons primarily determines the course of the disease. However, it has not yet been clarified why the development of cognitive and behavioural impairment during the course of ALS shortens survival. As we have shown in our study, it can only be partially explained by refusal of NIV. There is evidence of increased cortical and subcortical atrophy in patients with ALS

and cognitive and/or behavioural impairment.[65-68] One of the hypotheses for explaining the different patterns of atrophy among patients with pure motor signs and patients with concomitant cognitive and behavioural impairment includes differences in functional connectivity. There is evidence supporting a circuit-wise degeneration, leading to network failure.[66, 69] The involvement of different networks in ALS patients with cognitive and behavioural impairment compared to ALS patients with pure motor symptoms might therefore result in a faster disease progression. We therefore recommend future studies to focus on network analysis in cohorts of ALS, ALS-FTD and FTD patients in order to elucidate the degeneration of networks along the ALS-FTD disease continuum.

**Future directions**

In this thesis we have shown that the cognitive profiles of ALS and bvFTD show considerable overlap and consist of deficits in social cognition, fluency, executive functions and verbal memory. The most prominent behavioural changes in ALS are perseveration, apathy and disinhibition. However, as discussed before, there also seem to be differences between the cognitive and behavioural profiles of ALS and bvFTD, i.e. language impairment is part of the cognitive profile of ALS and disinhibition, dietary changes and inertia are reported to occur more frequently in bvFTD. In our studies we included groups of ALS-bvFTD and bvFTD patients, not only to serve as positive controls, but also to investigate the overlap between ALS and FTD. The sample size of these patients included in these groups, in particular ALS-bvFTD was quite small. Future studies should include larger groups of ALS, ALS-bvFTD and bvFTD patients in order to further elucidate the cognitive and behavioural overlap, but also clarify the differences between the two disease entities. As circuit-wise degeneration has been proposed as the underlying mechanism of symptomatology in ALS and FTD, brain networks in clinically well characterized ALS, ALS-bvFTD and FTD patients should be investigated. A comparison with pathological findings could help unravel the pathogenesis of these neurodegenerative diseases. We have taken the first step in this direction by performing a longitudinal network analysis study in ALS patients (pure motor ALS, ALS with mild cognitive and/or behavioural impairment and ALS-bvFTD), bvFTD patients and healthy controls. All participants underwent structural and functional MRI (diffusion tensor imaging and resting state functional MRI) and magnetoencephalography. The aim was to correlate degeneration of specific tracts with abnormalities in resting state networks across the ALS-FTD disease spectrum. The results of this study are currently being analysed.





***Survival in ALS patients with cognitive and behavioural impairment***

It has been suggested that motor neuron degeneration in ALS and ALS-FTD primarily determines disease progression. Therefore, one might argue that concurrent cognitive or behavioural impairment does not negatively influence survival. However, in one of our studies (**chapter 9**) we have shown reduced survival in prevalent patients with cognitive and behavioural impairment, including ALS-bvFTD, as compared to ALS patients with a pure motor variant. This finding could not be reproduced in an exploratory survival analysis in our larger cohort study of incident patients (cohort described in **chapter 6**, analysis not included in this thesis). This could be related to the fact that the median survival in the latter cohort was quite short (23 months) and there was not enough power to detect smaller differences. Also, ALS-bvFTD patients were excluded from this analysis. The influence of mild cognitive and behavioural impairment and their underlying specific network changes on survival therefore remains unclarified. We recommend future studies to include a larger group of both incident and prevalent ALS patients and examine survival not only related to cognitive and behavioural impairment, but also in association with network analysis.

***Quality of life in ALS patients with cognitive and behavioural impairment***

In this thesis we focused on the course of mild cognitive and behavioural impairment and the impact on survival. However, we did not investigate the influence on quality of life. There is ample literature about quality of life in ALS patients and their caregivers.[70-73] It has also been extensively shown that quality of life of FTD patients and their proxies is reduced.[74-76] However, there is a lack of studies investigating the impact of cognitive and behavioural impairment on quality of life in ALS patients and their caregivers.[77] One study did show reduced quality of life of the caregiver in the presence of behavioural changes.[27] Future studies should focus on the effects of cognitive and behavioural impairment on both the patient and their caregiver. Especially since a cure for ALS is probably not available in the near future, there should be a focus on symptomatic treatment and support in the ALS clinic, in order to maintain the highest possible quality of life. Psychological interventions are often used in ALS clinics, but there is a paucity of literature on the effect on quality of life.[78] Another method to improve cognitive and behavioural impairment might be found in pharmacology. The safety and effect of intranasal oxytocin on social impairment in FTD patients has been investigated and a positive effect on apathy and the expression of empathy was found, in combination with augmented activity in brain regions associated with social cognition.[9, 79] Investigations of other drugs for the improvement of behavioural symptoms in FTD, such as selective serotonin reuptake inhibitors and dopaminergic drugs have shown diverging or even negative results.[80, 81] The possible role of

psychological and pharmacological interventions in ALS patients with cognitive and behavioural impairment remains to be investigated.

## CONCLUSION

In this thesis we have established the cognitive profile of ALS and bvFTD and have provided further evidence for the existence of an ALS-FTD disease continuum. We developed the ALS-FTD-Q which has excellent clinimetric properties and is currently being used worldwide to screen for behavioural impairment in ALS patients. We also constructed a cognitive screening tool, but unfortunately the clinimetric properties were less convincing than expected and therefore, we do not recommend its use in ALS patients. Furthermore, we have shown that 30% of ALS patients has progression of cognitive and behavioural impairment during the course of their disease, and we also provided evidence for a reduced survival in these patients.

### Practical considerations for healthcare professionals in ALS clinics

1. Screening tools for cognitive and behavioural impairment in ALS patients are feasible and can be incorporated in the ALS clinic.
2. Neuropsychological tests should be adapted for use in ALS patients, to prevent overestimation of cognitive impairment.
3. When diagnosing a patient with ALS it can be informative to ask the proxy about memory impairment, to gain insight into the possible presence of cognitive impairment.
4. Cognitive and behavioural impairment can develop during the disease course and we therefore recommend repeated screening of every ALS patient.
5. When deficits in social cognition are suspected it can be advised to offer more psychological support to the caregiver.





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# APPENDICES

## SUMMARY

Cognitive and behavioural impairment are a key element of amyotrophic lateral sclerosis (ALS). There is evidence for the existence of a disease continuum with ALS and the behavioural variant of frontotemporal dementia (bvFTD) on both ends. In this thesis we aimed to develop screening instruments for cognitive and behavioural impairment in ALS that are free of bias due to motor and speech disturbances. In addition, we wanted to determine the profile and course of cognitive and behavioural impairment in early ALS patients.

**Part 1. Cognitive and behavioural impairment in ALS and behavioural variant FTD**
In the first part of this thesis we provided a systematic analysis and comparison of the cognitive profile of ALS and bvFTD. In **chapter 2** we updated a meta-analysis of the cognitive profile of ALS including 44 articles and 1287 non-demented ALS patients. Due to the large number of patients we were able to further establish the cognitive profile of ALS, which consists of deficits in fluency, language, social cognition, executive functions and verbal memory with sparing of visuoperception. In comparison to the previous meta-analysis from 2010 the confidence intervals of the effect sizes were much smaller and we discovered an important new cognitive domain, i.e. social cognition. Currently, social cognition is included in the criteria for cognitive impairment in ALS, which is at least partly due to our meta-analysis.

In **chapter 3** we performed a similar systematic review of the literature on cognition in bvFTD. The hallmark of bvFTD is progressive behavioural change, but cognitive impairment can also occur. We hypothesized that the cognitive profiles of ALS and bvFTD would show a significant overlap. We found that the cognitive profile of bvFTD consists of impairment in the domains social cognition, verbal memory, fluency and executive functions. Language had a relatively smaller effect size in bvFTD than in ALS and is therefore not part of the cognitive profile. This is probably caused by the exclusion of language variants of FTD (semantic dementia and primary progressive aphasia) from the meta-analysis. We found a high correlation coefficient of the cognitive profiles of ALS and bvFTD, which was even higher when the cognitive domain language was excluded. With these two meta-analyses we have provided further evidence for the existence of an ALS-FTD disease continuum.

Because behavioural changes are the key feature of bvFTD we wanted to investigate the frequency of behavioural impairment in ALS and explore the most commonly reported behavioural symptoms. In **chapter 4** we therefore presented a systematic review of the literature regarding behavioural changes





in ALS. We found that the most common behavioural changes include perseveration, apathy and disinhibition. The frequency of mild behavioural impairment in ALS was examined in eight studies and had a wide range from 17% to 88%. This is probably related to the use of different questionnaires to detect behavioural change, none of which were validated for use in ALS patients.

**Part 2. Screening for cognitive and behavioural impairment**
In the second part of this thesis we therefore aimed to develop screening instruments for cognitive and behavioural impairment in ALS patients. These screening instruments should not only account for impaired dexterity or slurred speech, but also for behavioural changes that are related to the process of grief and suffering from a chronic illness, in order to prevent overestimation of cognitive and behavioural impairment. One of the most frequently used cognitive tests in ALS patients is the verbal fluency task, as a measure of executive functions, in which the patient is asked to name as many words starting with the same letter in one minute. This test had previously been adapted to account for speech impairment in ALS patients. The adapted version, the verbal fluency index, calculates the thinking time per word. In **chapter 5** we provided normative data for the Dutch version of the verbal fluency index, corrected for age and educational level. Unfortunately, in our study we did not include the category fluency test (semantic fluency) and therefore normative data of this task are still lacking.

In **chapter 6** we presented the clinimetric properties of the ALS-FTD-Cognitive screen (ALS-FTD-Cog), a new screening instrument for cognitive impairment in ALS. Based on the meta-analysis presented in **chapter 2** we chose to include four tests, examining the domains social cognition, fluency, verbal memory and language. The clinimetric properties of our new screen were less than expected and also fell short of the Edinburgh Cognitive and Behavioural ALS Screen, which is currently a frequently used instrument worldwide. We therefore do not recommend the use of the ALS-FTD-Cog in ALS patients.

Based on our systematic review of behavioural changes in ALS we developed a behavioural questionnaire for ALS patients, the ALS-FTD-Questionnaire, which is described in **chapter 7**. The questionnaire consists of 25 items which need to be filled out by the proxy of the patient and requires about five to ten minutes. We not only included a large group of ALS patients and a healthy control group in the validation study, but also a group of ALS-bvFTD and bvFTD patients in order to determine the optimal cut-off value for severe behavioural changes. To account for behavioural changes related to chronic illness we also included patients with other neuromuscular diseases, such as inclusion body myositis,

which allowed us to determine the cut-off value for mild behavioural changes. Currently, the ALS-FTD-Q is a frequently used behavioural questionnaire in ALS clinics and research projects worldwide.

**Part 3. Course and implications of cognitive and behavioural impairment**

In the third part of this thesis we focused on the course of cognitive and behavioural impairment in a cohort of early ALS patients with a disease duration of less than twelve months. In **chapter 8** we presented the results of a cohort of 35 ALS patients who underwent a neuropsychological examination at baseline and at six months. With a loss-to-follow-up of only 20% we found evidence of progression of cognitive and behavioural impairment in ten patients (36%). In this study we have convincingly shown that cognitive and behavioural impairment can not only develop during the course of the disease but also progress in one-third of the patients. This finding indicates that screening for cognitive and behavioural change should be performed in all patients.

At the start of this thesis there was no compelling evidence of reduced survival in ALS patients with cognitive and behavioural impairment. In **chapter 9** we investigated the influence of cognitive and behavioural impairment, including FTD on survival in two cohorts of prevalent ALS patients (i.e. with diverging disease duration). We found robust evidence of reduced survival in ALS patients with cognitive and behavioural impairment, even in patients who initiated non-invasive ventilation. This finding emphasizes that cognitive and behavioural impairment in ALS have important consequences and should not be overlooked. In accordance with the current criteria for cognitive and behavioural impairment in ALS, we therefore recommend screening for cognitive and behavioural impairment in every ALS patient throughout the course of the disease.





## NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

Cognitieve stoornissen en gedragsveranderingen maken een belangrijk onderdeel uit van amyotrofische laterale sclerose (ALS). Er is bewijs voor het bestaan van een ziekte continuüm met ALS en frontotemporale dementie (FTD) aan beide uiteinden. In dit proefschrift hebben wij ons gericht op de ontwikkeling van screeningsinstrumenten die niet gehinderd worden door lichamelijke beperkingen of spraakstoornissen, voor het vaststellen van cognitieve stoornissen en gedragsveranderingen bij ALS patiënten.

**Deel 1. Cognitieve stoornissen en gedragsveranderingen bij ALS en gedragsvariant FTD**

In het eerste deel van dit proefschrift beschrijven wij een systematische analyse en vergelijking van het cognitieve profiel van ALS en gedragsvariant FTD. In **hoofdstuk 2** hebben wij een eerdere meta-analyse van het cognitieve profiel van ALS geactualiseerd, waarin 44 artikelen en 1287 niet-dementerende ALS patiënten zijn geïncludeerd. Door deze grote groep patiënten waren wij in staat om het cognitieve profiel van ALS nog genuanceerder te bepalen; het bestaat uit afwijkingen in fluency, taal, sociale cognitie, executieve functies en verbaal geheugen, waarbij visuoperceptie gespaard is. In vergelijking met de meta-analyse uit 2010 waren de betrouwbaarheidsintervallen rondom de effectgroottes een stuk kleiner en hebben wij een belangrijk nieuw cognitief domein toegevoegd, namelijk sociale cognitie. Dit domein is, mede door onze meta-analyse, sinds kort ook opgenomen in de criteria voor cognitieve stoornissen bij ALS.

In **hoofdstuk 3** hebben wij een vergelijkbare systematische analyse uitgevoerd van de literatuur over cognitie in gedragsvariant FTD. Het belangrijkste kenmerk van gedragsvariant FTD is een progressieve verandering van het gedrag, echter kunnen cognitieve stoornissen ook optreden. Wij veronderstelden dat de cognitieve profielen van ALS en gedragsvariant FTD een grote overlap zouden tonen. Wij stelden vast dat het cognitieve profiel van gedragsvariant FTD afwijkingen in sociale cognitie, verbaal geheugen, fluency en executieve functies omvat. Het domein taal had een relatief kleinere effectgrootte bij gedragsvariant FTD dan bij ALS en maakt daarom geen deel uit van het cognitieve profiel. Dit is waarschijnlijk veroorzaakt doordat wij patiënten met een taalvariant van FTD (semantische dementie en primair progressieve afasie) uit de meta-analyse hebben geëxcludeerd. Wij vonden een hoge mate van correlatie tussen de cognitieve profielen van ALS en gedragsvariant FTD, wat zelfs toenam na de exclusie van het taaldomein. Met deze twee meta-analyses hebben we aanvullend bewijs geleverd voor het bestaan van een ALS-FTD ziekte continuüm.

Aangezien veranderingen in gedrag het belangrijkste kenmerk zijn van gedragsvariant FTD wilden wij niet alleen de frequentie van deze gedragsveranderingen bij ALS onderzoeken, maar ook nagaan welke specifieke gedragsveranderingen het vaakst voorkomen. Daarom presenteren wij in **hoofdstuk 4** een systematisch overzicht van de literatuur over gedragsveranderingen bij ALS. De meest voorkomende gedragsveranderingen waren perseveratie, apathie en disinhibitie. De frequentie van lichte gedragsveranderingen bij ALS was onderzocht in acht studies en had een grote spreiding van 17% tot 88%. Dit is waarschijnlijk gerelateerd aan het gebruik van verschillende vragenlijsten om gedragsveranderingen vast te stellen, die geen van allen gevalideerd waren voor gebruik bij ALS patiënten.

**Deel 2. Screenen op cognitieve stoornissen en gedragsveranderingen**
In het tweede deel van dit proefschrift hebben wij ons gericht op de ontwikkeling van screeningsinstrumenten voor cognitieve stoornissen en gedragsveranderingen bij ALS patiënten. Deze screeningsinstrumenten moeten niet alleen rekening houden met verminderde behendigheid of onduidelijke spraak, maar ook met gedragsveranderingen die gerelateerd zijn aan het rouwproces en het lijden aan een chronische ziekte, om overschatting van cognitieve stoornissen en gedragsveranderingen te voorkomen. Een van de meest gebruikte cognitieve testen bij ALS patiënten is de verbale fluency test, als maat voor executieve functies, waarbij de patiënt gevraagd wordt zo veel mogelijk woorden met dezelfde beginletter op te noemen binnen een minuut. Deze test is al eerder aangepast zodat rekening wordt gehouden met spraakstoornissen van ALS patiënten. Deze aangepaste versie, de verbale fluency index, berekent de denktijd per woord. In **hoofdstuk 5** verschaffen wij normscores voor de Nederlandse versie van de verbale fluency index, gecorrigeerd voor leeftijd en opleidingsniveau. Helaas was de categorie fluency test (semantische fluency) niet in onze studie opgenomen, waardoor normscores voor deze test nog steeds ontbreken.

In **hoofdstuk 6** beschrijven wij de klinimetrische eigenschappen van de ALS-FTD-Cognitieve screen (ALS-FTD-Cog), een nieuw screeningsinstrument voor cognitieve stoornissen bij ALS. Gebaseerd op onze meta-analyse beschreven in **hoofdstuk 2** hebben wij ervoor gekozen om vier testen in de screen op te nemen, waarmee sociale cognitie, fluency, verbaal geheugen en taal worden onderzocht. De klinimetrische eigenschappen van ons nieuwe screeningsinstrument waren minder dan verwacht en waren daarnaast ook minder goed dan die van de Edinburgh Cognitive and Behavioural ALS Screen. Dit screeningsinstrument wordt tegenwoordig wereldwijd veel gebruikt. Wij bevelen het gebruik van de ALS-FTD-Cog daarom niet aan bij ALS patiënten.





Gebaseerd op onze systematische analyse van gedragsveranderingen bij ALS hebben we een gedragsvragenlijst ontwikkeld voor ALS patiënten, de ALS-FTD-Questionnaire, die wordt beschreven in **hoofdstuk 7**. De vragenlijst bestaat uit 25 items die door de naaste van de patiënt ingevuld worden en neemt ongeveer vijf tot tien minuten in beslag. We hebben niet alleen een grote groep ALS patiënten en gezonde controles geïncludeerd in de validatiestudie, maar ook een groep van ALS-FTD patiënten en gedragsvariant FTD patiënten zodat de optimale afkapwaarde voor ernstige gedragsveranderingen vastgesteld kon worden. Om rekening te kunnen houden met gedragsveranderingen gerelateerd aan het lijden aan een chronische ziekte hebben wij ook patiënten met andere spierziekten geïncludeerd, zoals inclusion body myositis. Hierdoor konden wij de optimale afkapwaarde voor lichte gedragsveranderingen bepalen. Momenteel is de ALS-FTD-Q wereldwijd een veel gebruikte gedragsvragenlijst in ALS klinieken en onderzoekprojecten.

**Deel 3. Beloop en gevolgen van cognitieve stoornissen en gedrags-veranderingen**
In het derde deel van dit proefschrift hebben wij ons gefocust op het beloop van cognitieve stoornissen en gedragsveranderingen in een cohort van 'vroege' ALS patiënten met een ziekteduur van minder dan twaalf maanden. In **hoofdstuk 8** bespreken wij de resultaten van een cohort van 35 ALS patiënten die zowel bij inclusie als na zes maanden een neuropsychologisch onderzoek hebben ondergaan. Met een uitval van slechts 20% na zes maanden hebben wij bewijs gevonden van progressie van cognitieve stoornissen en gedragsveranderingen in tien patiënten (36%). In deze studie tonen wij overtuigend aan dat cognitieve stoornissen en gedragsveranderingen niet alleen kunnen ontstaan tijdens het ziektebeloop, maar ook kunnen verergeren bij een derde van de patiënten. Deze bevinding duidt aan dat alle ALS patiënten gescreend moeten worden op cognitieve stoornissen en gedragsveranderingen.

Aan het begin van het onderzoek dat wordt beschreven in dit proefschrift was er geen overtuigend bewijs voor kortere overleving van ALS patiënten met cognitieve stoornissen en gedragsveranderingen. In **hoofdstuk 9** hebben wij daarom de invloed van cognitieve stoornissen en gedragsveranderingen, waaronder ook FTD, onderzocht in twee cohorten van prevalente ALS patiënten (dat wil zeggen patiënten met een variërende ziekteduur). Wij vonden robuust bewijs voor een kortere overleving van patiënten met cognitieve stoornissen en gedragsveranderingen, zelfs bij patiënten die waren gestart met non-invasieve beademing. Deze bevinding benadrukt dat cognitieve stoornissen en gedragsveranderingen belangrijke gevolgen hebben en daarom niet over het hoofd gezien moeten worden. In overeenstemming met de geldende criteria voor cognitieve stoornissen en gedragsveranderingen bij ALS adviseren wij

daarom om alle ALS patiënten gedurende hun ziektebeloop te screenen op cognitieve stoornissen en gedragsveranderingen.





## ABBREVIATIONS

| | |
|---|---|
| ACE-R: | Addenbrooke's cognitive evaluation – revised |
| ALS: | amyotrophic lateral sclerosis |
| ALSbi: | ALS with behavioural impairment |
| ALS-CBS: | ALS cognitive behavioral screen |
| ALSci: | ALS with cognitive impairment |
| ALSFRS-R: | ALS functional rating scale – revised |
| ALS-FTD: | amyotrophic lateral sclerosis – frontotemporal dementia |
| ALS-FTD-Cog: | amyotrophic lateral sclerosis – frontotemporal dementia – cognitive screen |
| ALS-FTD-Q: | amyotrophic lateral sclerosis – frontotemporal dementia – questionnaire |
| ALSSS: | ALS severity scale |
| AMC: | academic medical center |
| ANOVA: | analysis of variance |
| AUC: | area under the curve |
| AVLT: | auditory verbal learning test |
| Aβ42: | amyloid beta 42 |
| b: | bulbar onset |
| BDI: | Beck depression inventory |
| BI: | behavioural impairment |
| BNT: | Boston naming test |
| BPVS: | British picture vocabulary scale |
| BTO(T): | Benton temporal orientation test |
| Bv-FTD: | behavioural variant – frontotemporal dementia |
| C9orf72: | chromosome 9 open reading frame 72 |
| CBI-R: | Cambridge behavioural inventory – revised |
| CDR: | clinical dementia rating scale |
| CI: | confidence interval *or* cognitive impairment |
| CSF: | cerebrospinal fluid |
| DART: | Dutch adult reading test |
| ECAS: | Edinburgh Cognitive and Behavioural ALS Screen |
| FAB: | frontal assessment battery |
| FBI(-ALS): | frontal behavioural inventory (– ALS) |
| FCSRT: | free and cued selective reminding test |
| f-FTD: | frontal variant frontotemporal dementia |
| FPT: | faux pas test |
| FrSBe: | frontal systems behavior scale |
| FS: | frontotemporal syndrome |
| FTD: | frontotemporal dementia |
| FTD-FRS: | FTD – functional rating scale |

| | |
|---|---|
| FTLD: | frontotemporal lobar degeneration |
| FUS: | RNA binding protein Fused in Sarcoma |
| FVC: | forced vital capacity |
| HADS: | hospital anxiety and depression scale |
| HC: | healthy controls |
| HR: | hazard ratio |
| IGT: | Iowa gambling test |
| ISCED: | international standard classification of education |
| JOLO: | judgment of line orientation |
| l: | limb onset |
| lb: | limb and bulbar onset |
| LNS: | letter number sequencing |
| MAPT: | microtubule-associated protein tau |
| MDRS: | Mattis dementia rating scale |
| MiND-B: | motor neuron disease behaviour scale |
| MMSE: | mini mental state examination |
| MND: | motor neuron disease |
| MND-(bv)FTD: | motor neuron disease – (behavioural variant) frontotemporal dementia |
| MOCA: | Montreal cognitive assessment |
| MTL: | medial temporal lobe |
| N: | number |
| NA: | not applicable |
| ng: | not given |
| NIV: | non-invasive ventilation |
| NOS: | Newcastle—Ottawa quality assessment scale |
| NPE: | neuropsychological examination |
| NPI: | neuropsychiatric inventory |
| PAN: | population-based epidemiological ALS-study in the Netherlands |
| PET: | positron emission tomography scan |
| PGRN: | progranulin |
| PLS: | primary lateral sclerosis |
| PMA: | progressive muscular atrophy |
| PPTT: | pyramid and palm trees test |
| PPVT: | Peabody picture vocabulary test |
| PSSFTS: | Penn state screening examination of frontal and temporal dysfunction syndromes |
| p-τ: | phosphorylated tau |
| RAVLT: | Rey auditory verbal learning test |
| RBMT: | Rivermead behavioral memory test |
| RCF: | Rey complex figure test |
| RME: | reading the mind in the eyes test |
| RMT: | recognition memory test |
| SD: | standard deviation |
| SDMT: | symbol digit modalities test |
| SDST: | symbol digit substitution test |
| SOD1: | superoxide dismutase 1 |
| SYDBAT: | Sydney language battery |
| TASIT: | the awareness of social inference test |
| TDP43: | TAR DNA-binding protein |
| TMT: | trail making test |
| ToM: | theory of mind |
| UCSF-SB: | University of California San Francisco – screening battery |
| VFI: | verbal fluency index |
| VOSP: | visual object and space perception battery |
| w/o: | without |
| WAB: | Western aphasia battery |
| WCST: | Wisconsin card sorting test |
| τ: | tau |
| %pred: | percentage of predicted |
| %predVC: | percentage of predicted forced vital capacity |
| VAT: | visual association test |
| WAIS: | Wechsler adult intelligence scale |

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| *Poster presentation* | | |
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Collega's van Z-0.
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Mijn kamergenoten op H2-235.
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